Welcome to this autumn issue of Respiratory Research Review on the topic of pneumonia and influenza – by the time you are reading this issue, we will have had our yearly influenza vaccinations and offered it to our vulnerable patients. We now need to hope that the strains chosen for the vaccination will be closely matched to the strains that will be in circulation this year. We are reviewing one of the articles from two separate research groups that are working on a vaccine against the highly conserved stem region of the haemagglutinin glycoprotein. If their research ambition were to be successful, this vaccination would not only offer long-term protection, it would also protect against unrelated subtypes, including types arising from avian or swine reservoirs. We also continue to think about the PCV (pneumococcal conjugate vaccine), which appears effective in protecting children in South Africa and cost effective in the Netherlands, although still rather expensive. However, Michael Hochman and Pieter Cohen (JAMA Intern Med) argue it may provide little additional protection in communities, like the US or NZ, where children have been vaccinated. Talha Khan Burki (Lancet Respir Med) argues the vaccine is far too expensive, and Mathias Pietz and Tobias Welte (Eur Respir J) reflect that vaccine provision is more an ethical-political than a scientific-economical question.

Last year we expressed the opinion that the use of prednisone in severe pneumonia is probably coming of age, which has led to some debate. The jury is still out; however, clinicians may find some reassurance in the finding of a systematic review and meta-analysis suggesting that short-term steroids may be safe and may reduce the risk of acute respiratory distress syndrome and shorten the length of hospital stay (Crit Care 2016;19:11279–119). Paracetamol, on the other hand, has not been shown to reduce temperatures or alleviate clinical symptoms during an influenza infection (Respirology). A French group using low-dose CT scanning (a radiation dose similar to two chest x-rays) demonstrated that about a third of patients thought to have pneumonia on chest x-ray don’t have one on CT; a further third without pneumonia on chest x-ray do have one on CT. Do we need to rethink our diagnostic algorithms?

We sincerely hope you enjoy the selection of articles in this autumn selection. The interested reader may enjoy the beautifully written series on pleural diseases – past, present and future direction (Eur Respir J). Professor Lutz Beckert (Lancet Respir Med 2015;3:37(1):563–77) argue it may provide little additional protection in communities, like the US or NZ, where children have been vaccinated. We now need to hope that the strains chosen for the vaccination will be closely matched to the strains that will be in circulation this year. We are reviewing one of the articles from two separate research groups that are working on a vaccine against the highly conserved stem region of the haemagglutinin glycoprotein. If their research ambition were to be successful, this vaccination would not only offer long-term protection, it would also protect against unrelated subtypes, including types arising from avian or swine reservoirs. We also continue to think about the PCV (pneumococcal conjugate vaccine), which appears effective in protecting children in South Africa and cost effective in the Netherlands, although still rather expensive. However, Michael Hochman and Pieter Cohen (JAMA Intern Med) argue it may provide little additional protection in communities, like the US or NZ, where children have been vaccinated. Talha Khan Burki (Lancet Respir Med) argues the vaccine is far too expensive, and Mathias Pietz and Tobias Welte (Eur Respir J) reflect that vaccine provision is more an ethical-political than a scientific-economical question.

Abbreviations used in this issue
CAP = community-acquired pneumonia
CT = computed tomography
HIV = human immunodeficiency virus
PCR = polymerase chain reaction
PCV = pneumococcal conjugate vaccine
PEEP = positive end-expiratory pressure
Randomized controlled trial of the effect of regular paracetamol on influenza infection

Authors: Jeffries S et al., and on behalf of the PI study group

Summary: Eighty adults with influenza-like illness and positive influenza rapid antigen tests were randomised to receive paracetamol (acetaminophen) 1g four times daily or placebo for 5 days; 24 and 22 participants from the respective groups were influenza PCR-positive. No significant difference was seen between the paracetamol and placebo arms for mean area under the curve for quantitative PCR log₂, viral load from baseline to day 5 (primary outcome; 4.64 vs. 4.40 [p=0.36]), symptom score, temperature, time to resolution of illness or health status; there was no evidence of an interaction between randomised treatment and detection of influenza virus on PCR.

Comment: In animals, treatment with antipyretics increases mortality of viral infections; in humans, paracetamol prolongs infection with varicella zoster, malaria and rhinovirus. Our colleagues from Wellington went out to explore whether paracetamol use may prolong viral shedding, thereby worsening symptoms and prolonging illness during an influenza infection. The study turned out to be a little underpowered; however, reassuringly it found no significant difference in viral loads between the paracetamol and placebo groups. Bottom line: paracetamol did not reduce temperature or alleviate the clinical symptoms. There remains an insufficient evidence base for paracetamol in influenza infection.


Abstract

Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection

Authors: Yassine HM et al.

Summary: These authors reported the structure-based development of an H1 haemagglutinin stem-only immunogen that conferred heterosubtypic protection in mice and ferrets. H1 haemagglutinin stabilised-stem immunogens that lack the immunodominant head domain were obtained with six iterative cycles of structure-based design. Preservation of key structural elements was confirmed. Mice were completely, and ferrets partially, protected against lethal heterosubtypic H5N1 influenza virus challenge by broadly cross-reactive antibodies following vaccination with H1 haemagglutinin stabilised-stem immunogens on ferritin nanoparticles, despite the absence of detectable H5N1 neutralising activity in vitro. Passive immunoglobulin transfer from vaccinated to nonvaccinated mice conferred protection against H5N1 challenge, indicating that vaccine-elicited haemagglutinin stem-specific antibodies are able to protect against diverse group 1 influenza strains.

Comment: At least two major research groups are working on a possible vaccine targeting the highly conserved haemagglutinin glycoprotein stem region, which doesn’t undergo the seasonal antigen drift. This US-based group reports on a structure-based design process to circumvent an immune response to the highly variable head region. They employed a nanoparticle antigen-display platform to elicit an antibody response against the stable hemagglutinin glycoprotein stem. Mice and ferrets were protected against H1N1 and H5N1 infection. Bottom line: this proof-of-concept study demonstrates that the development of a vaccine against the hemagglutinin glycoprotein stem region is possible and confers wide protection.

Reference: Nature Medicine 2015;21(9):1065–70

Abstract

Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination

Authors: Grijalva CG et al.

Summary: These researchers used EPIC study data to explore the association between influenza vaccination status and hospitalisation for laboratory-confirmed influenza-associated CAP; 162 cases aged ≥6 months were compared with 2605 control participants who had been vaccinated against influenza. Of the remaining 2605 participants who had not been vaccinated against influenza, 28 (17%) of these participants they could prove influenza as the cause of the CAP; 28 (17%) of these participants had been vaccinated against influenza. Of the remaining 2605 participants admitted with influenza-negative pneumonia, 766 (29%) had been vaccinated. Bottom line: influenza vaccination seemed to protect against influenza pneumonia with a vaccine effectiveness of about 60%.

Comment: In this article, the authors used the data of 2767 patients admitted with CAP. In 162 of these participants, they could prove influenza as the cause of the CAP; 28 (17%) of these participants had been vaccinated against influenza. Of the remaining 2605 participants admitted with influenza-negative pneumonia, 766 (29%) had been vaccinated. Bottom line: influenza vaccination seemed to protect against influenza pneumonia with a vaccine effectiveness of about 60%.


Abstract

Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

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*LAMA = Long-acting muscarinic antagonist, LABA = Long-acting beta 2 agonist, TAPS GA187115/SHMAUC100269/16

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Influenza virus damages the alveolar barrier by disrupting epithelial cell tight junctions

Authors: Short KR et al.

Summary: An in vitro coculture model was used to investigate damage to the pulmonary epithelial-endothelial barrier caused by influenza A virus. Human epithelial and endothelial cells seeded on the upper and lower halves of a transwell membrane, respectively, were grown in coculture with influenza A virus added to the upper chamber. There was significant epithelial-endothelial barrier damage on the addition of H1N1 and H5N1 influenza A virus subtypes. Of note, such damage occurred independently of endothelial cells even though the endothelial cells mounted a pro-inflammatory/procoagulant response to the viral infection in the adjacent epithelial cells. Moreover, barrier damage was found to be associated with tight junction disruption among epithelial cells and loss of tight junction protein claudin-4.

Comment: Influenza A typically causes acute upper respiratory tract infection; however, it can also cause viral pneumonia and, at times, acute respiratory distress syndrome by damaging the epithelial-endothelial barrier and flooding the alveolar airspaces with fluid, erythrocytes and leucocytes preventing gas exchange. This Dutch research group demonstrated in an in vitro model that this flooding is not caused by cell death; it is caused by loss of integrity of the epithelial tight junction, specifically the loss of the tight junction protein claudin-4. Bottom line: the understanding that the influenza virus targets the epithelial cell junction will lead to new therapeutic approaches and interventional strategies.


Abstract

Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications

Authors: Ladha K et al.

Summary: This hospital-based registry study assessed the effect of the intraoperative use of protective mechanical ventilation on major postoperative respiratory complications. They also sought to define safe intraoperative mechanical ventilator settings that do not translate into an increased risk of postoperative respiratory complications. Records were reviewed from 69,265 US adults who underwent general anaesthesia with endotracheal intubation. Protective ventilation was defined as a median PEEP of ≥5cm H2O, a median tidal volume of <10 mL/kg and a median plateau pressure of <70 cm H2 O. A total of 34,800 patients (50.2%) received protective ventilation and 34,465 (49.8%) received nonprotective ventilation intraoperatively. With a median PEEP of ≥5 cm H2O, a median tidal volume of less than 16 mL/kg and median plateau pressures of ≤16 cm H2O were identified as having the lowest risk of postoperative respiratory complications.

Comment: One way to protect the alveolar spaces will be by reducing the stress created among epithelial cells and loss of tight junction protein claudin-4. Influenza A typically causes acute upper respiratory tract infection; however, it can also cause viral pneumonia and, at times, acute respiratory distress syndrome by damaging the epithelial-endothelial barrier and flooding the alveolar airspaces with fluid, erythrocytes and leucocytes preventing gas exchange. This Dutch research group demonstrated in an in vitro model that this flooding is not caused by cell death; it is caused by loss of integrity of the epithelial tight junction, specifically the loss of the tight junction protein claudin-4. Bottom line: the understanding that the influenza virus targets the epithelial cell junction will lead to new therapeutic approaches and interventional strategies.

Reference: BMJ 2015;351:h3846

Abstract

Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands

Authors: Mangen MJ et al.

Summary: These authors used Markov-type modelling to determine incremental cost-effectiveness ratios associated with PCV-13 (13-valent PCV) use in adults from the Netherlands. A base case of PCV-13 vaccination in adults aged 65–74 years was compared with no vaccination, assuming no net indirect effects in the base case due to paediatric 10-valent PCV use. The authors also performed analyses for age- and risk-group specific vaccination strategies and for different levels of hypothetical herd effects from a paediatric PCV programme. The base case was associated with an incremental cost-effectiveness ratio of €8650 per quality-adjusted life-year. Vaccinating high-risk individuals aged 65–74 years saved costs, and extension to medium-risk individuals aged 65–74 years was associated with an incremental cost-effectiveness ratio of €2900. Further extension to medium- and high-risk adults (aged ≥18 years) was associated with an incremental cost-effectiveness ratio of €3100.

Comment: The CAPiTA study (Respiratory Research Review, issue 101) demonstrated that the PCV-13 reduced CAP in elderly subjects with organisms covered by the vaccine, with a vaccine efficacy of 46%. It is estimated that the vaccine efficacy against all CAP is about 5%, it didn’t reduce the mortality due to pneumococcal disease. The authors use data from the CAPiTA study to demonstrate that PCV13 would be cost effective in the Netherlands. Mathias Pletz and Tobias Welte in their editorial give us the bottom line: these Dutch data are difficult to apply to populations with a good PPV-23 (23-valent polysaccharide vaccine) coverage and childhood vaccination of PCV-13.

Reference: Eur Respir J 2015;46(8):1407–16

Abstract

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Effectiveness of pneumococcal conjugate vaccine against presumed bacterial pneumonia hospitalisation in HIV-uninfected South African children

Authors: Madhi SA et al.

Summary: The effectiveness of 7- or 13-valent PCV was assessed against hospitalisation for presumed bacterial pneumonia (WHO-defined, radiographically confirmed pneumonia or ‘other infiltrate’ on chest x-ray with C-reactive protein level ≥40 mg/L) in 1326 South African children without HIV versus 2075 matched controls hospitalised with a disease unlikely to be pneumococcal and also in 889 cases versus 2628 matched community controls. The respective adjusted vaccine effectiveness values of an up-to-date PCV schedule in children aged >8 weeks and 16–103 weeks were 20.1% and 39.2% compared with the hospital controls and 32.1% and 38.4% compared with the community controls.

Comment: These South African authors used a case-control design to estimate the PCV-13 vaccine efficiency in children; a very laudable initiative given that about 450,000 children die of pneumococcal disease each year. Children admitted to three South African hospitals with probable bacterial pneumonia were matched with hospital and community controls without pneumonia. The authors estimated a vaccine efficiency of about 40%, which is similar to the efficiency observed in randomised controlled trials. The accompanying editorial provides an excellent context of these findings. Bottom line: the vaccination seems effective; however, we also need to tackle risk factors like maternal smoking, poor nutrition and overcrowding.


Abstract

Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia

Authors: Claessens Y-E et al.

Summary: This prospective research included 319 patients with clinically suspected CAP who underwent multidetector chest CT scan within 4 hours of presenting to an emergency department; 188 participants had parenchymal infiltrates on chest x-ray. Before CT scan results became available, CAP was classified as definite and probable/possible in 44.8% and 58.8% of the participants, respectively, and was excluded in 1.2%. CT scans revealed parenchymal infiltrates in 33% of the participants without an infiltrate on chest x-ray, and excluded CAP in 29.8% of those with parenchymal infiltrate on chest x-ray. Classifications were modified by CT scan results in 58.6% of the participants, with definite CAP in 50.8% and CAP excluded in 28.8%; 80% of the modifications were in accordance with an adjudication committee’s classifications. CT scan results led to initiation and discontinuation of antibiotics in 16% and 9% of participants, respectively, and hospitalisation and discharge in 22 and 23 participants, respectively.

Comment: CAP is diagnosed based on infective symptoms and chest x-ray infiltrates. This French group performed a low-dose CT scan in about 300 patients admitted with CAP. Following the CT scan, the emergency physician revised the probability of CAP in more than half of all cases – in particular about 30% of participants with CAP on the chest x-ray didn’t have it on the CT scan. Also, about 30% who had no chest x-ray changes had pneumonia on the CT scan. Bottom line: we need to embark on studies to explore if the higher accuracy of CT scans improves clinical outcomes.

Reference: Am J Respir Crit Care Med 2015;192(8):974–82

Community-acquired pneumonia requiring hospitalization among U.S. adults

Authors: Jain S et al., for the CDC EPIC study team

Summary: This population-based surveillance for CAP requiring hospitalisation enrolled 2488 eligible US adults. Among patients with radiographical evidence of pneumonia (n=2320), median age was 57 years, 21% required intensive care and the mortality rate was 2%. Among patients with radiographical evidence of pneumonia and specimens available for both bacterial and viral testing (n=2259), 38% had a pathogen detected, including 23% with >1 virus, 11% with bacteria, 3% with bacterial and viral pathogens and 1% with a fungal or mycobacterial pathogen. The most common pathogens were human rhinovirus (9%), influenza virus (6%) and Streptococcus pneumoniae (5%). Pneumonia occurred at an annual incidence of 24.8 per 10,000, with high incidences in patients aged 65–79 years (63.0 per 10,000) and those aged ≥80 years (164.3 per 10,000); the incidence also increased with age for each pathogen.

Comment: We have mentioned the CDC EPOC study on about 2500 adults with pneumonia earlier. The authors systematically investigated all admissions with pneumonia for a possible underlying organism using blood, sputum, endotracheal aspirates, bronchoalveolar lavage, pleural fluid and nasopharyngeal swabs as and when possible and appropriate. Despite all these efforts, no causative organism was found in 62% of cases. The three most common causes of pneumonia were rhinovirus infection, influenza A or B and S. pneumoniae. The incidence of pneumonia increased significantly with advancing age. Bottom line: no organism was identified in most cases; respiratory viruses were detected more frequently than bacteria.


Abstract
Ten-year mortality after community-acquired pneumonia

Authors: Euriaich DT et al.

Summary: These researchers followed a prospective cohort of 6078 adults with CAP (56% outpatients) and 29,402 controls without pneumonia in Canada for adverse long-term outcomes over a median 9.8 years. Compared with the controls, the patients with CAP were more likely to die (absolute risk difference 30 per 1000 patient-years; adjusted hazard ratio 1.65 [95% CI 1.57, 1.73]) or require an emergency department visit, hospitalisation for any cause or a CAP-related visit (p<0.001 for all). Patients with CAP aged <25 years had the lowest absolute rate difference for mortality at 4 per 1000 patient-years, while the highest absolute rate difference of 92 per 1000 patient-years was seen in those aged >80 years.

Comment: The Canadian authors reported approximately 10 years of follow-up data of 6000 patients with CAP, who were matched with up to five age- and sex-matched controls. The key finding is that patients who experienced one episode of CAP had significantly higher mortality and morbidity rates irrespective of their age. The three most common causes of death were due to the circulatory system, neoplasm and respiratory system – patients with previous CAP had more than twice the all-cause mortality compared with controls. Bottom line: the increased risk of death should assist discharge planning and considering preventive strategies.


Abstract

Cardiovascular outcomes associated with use of clarithromycin

Authors: Wong AYS et al.

Summary: This population-based study examined the association between clarithromycin use and CV outcomes in patients treated for Helicobacter pylori eradication. Patients living in Hong Kong who received clarithromycin (n=108,988) or amoxicillin (n=217,753) during 2005–2009 were included. A case-control analysis showed that clarithromycin was associated with an increased risk of myocardial infarction within 14 days after the start of treatment compared with amoxicillin (44.4 vs. 19.2 events per 1000 person-years; propensity score-adjusted rate ratio 3.66 [95% CI 2.82, 4.76]). In a self-controlled case analysis, current use of clarithromycin for H. pylori eradication was associated with CV events, but the risk returned to baseline after treatment had ended.

Comment: In the absence of an identified organism, the clinician needs to decide how to treat pneumonia based on the clinical presentation, as early treatment has been shown to improve survival (Horne). This study from Hong Kong and London identified CV outcomes in about 100,000 patients treated with clarithromycin compared with about 200,000 patients treated with amoxicillin in the period 2005–2009. Current use of clarithromycin was associated with an almost doubled incidence of myocardial infarction, arrhythmias and cardiac mortality. No long-term risks were identified. Bottom line: clarithromycin should be prescribed with caution, particularly in patients with high baseline CV risk.

Reference: BMJ 2016;352:h6926

Abstract

Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices

Authors: Meeker D et al.

Summary: In this trial, 248 clinicians from 47 US primary-care practices were randomised by cluster to receive 0, 1, 2 or 3 behavioural interventions for 18 months. At study entry, all participants received education on antibiotic prescribing guidelines and strategies. Intervention arms included: i) order set prompting antibiotic use; ii) antibiotic prescribing for respiratory tract infections; and iii) peer comparison (clinicians were sent emails that compared their antibiotic prescribing rates with those with the lowest prescribing rates that failed to meet guidelines). Antibiotic prescribing rates for visits with antibiotic-inappropriate diagnoses (non-specific upper respiratory tract infections, acute bronchitis and influenza) were analysed from 18 months preintervention to 18 months afterward. There were 14,753 visits at baseline for antibiotic-inappropriate acute respiratory tract infections and 16,959 visits during the intervention period. Mean prescribing rates decreased from 24.1% at the start of the intervention to 13.1% at month 18 for control practices, from 22.1% to 6.1% for suggested alternatives (p=0.06 for differences in trajectories), from 23.2% to 5.2% for accountable justification (p<0.001) and from 19.9% to 3.7% for peer comparison (p<0.001).

Comment: This study is probably more relevant in an American setting. The study starts with the statement that antibiotics are overused, exposing patients to increased risk of adverse events, driving the healthcare cost up and increasing resistance. The authors selected 49 primary-care practices and compared the effectiveness of three different strategies to reduce antibiotic prescribing: a) electronic prompted suggestions of nonantibiotic treatments; b) free-text justification of antibiotic prescribing in the electronic record; and c) the most effective regimen, our bottom line: a weekly email comparing the prescribing habits to peers including the proportion of antibiotics prescribed. Now, here is a challenge for a peer group meeting.

Reference: JAMA 2016;315(6):562–70

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Diabetes & Obesity Research Review Issue 104

Key points from the review:

• Need to encourage all adolescents to exercise regularly due to long-term risk of obesity and lack of fitness & CV risk later in life.
• Reducing weight gain (even modest weight loss) in high-risk individuals (including rural women) does reduce rates of type 2 diabetes.
• Structured self-management education programmes are an important part of a quality diabetes service and help to reduce emergency diabetes-related incidences.

Application to my practice:

Making time to work with people towards manageable, realistic and incremental lifestyle adjustments has considerable benefits in terms of managing diabetes and reducing CV risk.

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