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Present and future of lung cancer immunotherapy

NAOMI RODRIG

The development of immunotherapy and recent approval of agents which block various components of the immune checkpoint pathway, such as programmed cell death-1 (PD-1) receptor and its ligand PD-L1, have revolutionized lung cancer treatment.

“The PD-1 inhibitor nivolumab was approved in March 2015 for advanced squamous non-small-cell lung cancer [NSCLC] that has progressed on platinum-based chemotherapy, and in October 2015 the approval was expanded to non-squamous NSCLC,” said Dr. Martin Reck of the Lung Clinic Grosshansdorf, Germany, at the European Lung Cancer Conference (ELCC) 2016 held recently in Geneva, Switzerland. “Data from two phase III trials showed that second-line nivolumab prolonged overall survival [OS] vs docetaxel in patients with squamous and non-squamous tumours.”

Shortly afterwards the US FDA approved another PD-1 antibody, pembrolizumab, which prolonged OS vs docetaxel in patients with PD-L1-positive NSCLC. [Lancet 2015;387:1540-1550] The PD-L1 antibody atezolizumab has also shown activity in patients with refractory NSCLC, regardless of the number of prior therapies. [ECC 2015, abstract 16LBA]


Current immunotherapy research is focusing on combining PD-1 and PD-L1 inhibitors with various treatment modalities, such as chemotherapy and targeted therapies. Of special interest is their combination with other monoclonal antibodies such as ipilimumab and tremelimumab, which target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), another immune checkpoint receptor on T cells. While predicted to have greater antitumour activity than either agent alone, concerns have been raised about the intolerable overlapping toxicity profile of those combinations.

Recently, a phase Ib trial of tremelimumab
and the PD-L1 antibody durvalumab in advanced NSCLC has identified a dose combination with a manageable safety profile and a response rate (RR) of 23 percent. [Lancet Oncol 2016;17:299-308]

With the positive results of immunotherapy in unselected patient populations, studies are now searching for biomarkers to improve patient selection and treatment monitoring. The nivolumab trials showed that PD-L1 expression levels were positively correlated with improved RRs and OS in non-squamous NSCLC, but not in squamous disease.

“Potential biomarkers of response include PD-L1 expression on tumour and immune cells, CD8+ T cell infiltrates and tumour mutational burden,” said Dr. John Haanen of the Netherlands Cancer Institute, Amsterdam, The Netherlands, in his keynote lecture. “While these approaches seem promising, we have to consider the limitations of PD-L1 expression as a biomarker. PD-L1 expression is dynamic and heterogeneous within tissue, and it’s unclear what level of PD-L1 is important. Further studies will define the optimal role for PD-L1 expression testing and other biomarkers to guide patient selection for immunotherapy and help monitoring.”

Blood test gains credence for tumour genotyping

NAOMI RODRIG

Several new studies presented at the European Lung Cancer Conference (ELCC) 2016 have confirmed the benefit of plasma circulating tumour DNA (ctDNA) testing for EGFR mutation analysis to predict treatment benefit of targeted therapies for non-small-cell lung cancer (NSCLC). Tissue biopsy, the gold standard for tumour genotyping, is not feasible in about 20 percent of patients, and plasma biomarkers are a potential alternative.

Previous data from the ASSESS trial demonstrated an 89 percent concordance for EGFR mutation detection between tumour biopsy and plasma ctDNA in matching samples from over 1,000 NSCLC patients. [ELCC 2015, abstract 350_PR] Now, an updated analysis reveals that increased sensitivity of EGFR mutation detection is associated with an increasing number of organs with metastases and a higher metastatic
grade. [ELCC 2016, abstract 58O_PR]

“The improved ability to detect mutations in plasma from patients with more metastases makes sense biologically, as these patients have higher tumour burden and we could expect more ctDNA to be released in the blood,” remarked Dr. Nicola Normanno of the INT-Fondazione Pascale, Naples, Italy, who reported the results.

In another study, plasma samples were collected from NSCLC patients with T790M mutation enrolled in two phase II studies (AURA2 and AURA extension) that assessed the efficacy of osimertinib – a third-generation tyrosine kinase inhibitor (TKI) which targets the T790 resistance mutation as well as common EGFR mutations sensitive to EGFR-TKIs. [ELCC 2016, abstract 134O_PR]

“In the pooled analysis, the positive percentage agreement and negative percentage agreement between the tissue and plasma tests for T790M detection were 61.4 and 78.6 percent, respectively. Patients with either positive T790M test also had a comparable overall response rate to the drug,” reported Dr. James Yang of the National Taiwan University, Taipei, Taiwan. “Our data indicate that around 60 percent of patients with T790M-positive NSCLC could have avoided an invasive biopsy by using a plasma ctDNA test. For EGFR-TKI-resistant patients without detectable T790M in plasma, a tissue biopsy is advised to rule out false negatives from the plasma test.”

A third study, which assessed the effectiveness of osimertinib based on tumour or plasma genotyping results of patients from the phase I AURA trial, found a concordance of 70-80 percent between the tests for T790M detection. [ELCC 2016, abstract 135O_PR]

“Patients with T790M-positive results from either tumour or plasma had high response rates and long progression-free survival on osimertinib,” said lead author Dr. Geoffrey Oxnard of the Dana-Farber Cancer Institute in Boston, MA, US. “Although the noninvasive blood test appears to detect T790M-positive patients very effectively, the false negative rate is 20-30 percent. We recommend a two-staged approach: Those who test positive for T790M in plasma can receive osimertinib; those who test negative should have their T790M status clarified by biopsy testing before treatment selection.”
Breast conserving therapy linked to local cancer recurrence in young women

ROSHINI CLAIRE ANTHONY

Young breast cancer patients who undergo breast conserving therapy (BCT) and radiation therapy may be at a higher risk of local cancer recurrence compared to those who undergo a mastectomy and no radiation, according to a study presented at the recent European Society for Radiotherapy and Oncology conference (ESTRO35) 2016, held in Turin, Italy.

Young women (aged <45 years) with early stage breast cancer and no lymph node involvement who underwent BCT and radiation had a 13 percent higher risk of local recurrence over a 20-year period than women who underwent a mastectomy and no radiation. [ESTRO35 2016, abstract OC-0052]

Among the younger patients, local recurrence was a predictor of distant metastasis (hazard ratio [HR] 2.0), an association not observed in older patients (>45 years; HR 0.9). The 20-year breast cancer-related mortality and overall mortality was also higher in young women who underwent BCT (HR 1.6 for breast cancer mortality and HR 1.7 for overall mortality).

In women who underwent mastectomy, local recurrences mostly occurred in the first 5 years after treatment for older women and within the first 10 years for younger women, while patients who had undergone BCT developed local recurrence throughout the follow-up period regardless of age.

“We found that among patients older than 45 years receiving BCT, local recurrence was not associated with distant metastasis and the 20-year mortality was not different between BCT and mastectomy,” said study author Dr. Tinne Laurberg from the Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, who presented the results.

“These findings are in line with long-term data reported from several randomized trials, confirming that it is safe to offer older, lymph...
Prognostic factors play an important role in endometrial cancer treatment decisions

KAVITHA G. SHEKAR

Prognostic factors such as tumour histology, tumour grade, and FIGO (Federation of International of Gynaecologists and Obstetricians) stage play an important role in endometrial cancer (EC) treatment outcomes, and should be considered while making treatment decisions, say researchers at the recently held meeting of the European Society for Radiotherapy and Oncology (ESTRO35), Turin, Italy.

To analyse the impact prognostic factors had on EC patients, the researchers studied the disease free survival (DFS) and overall survival (OS) of patients who underwent adjuvant radiotherapy. A total of 155 patients aged 31 to 86 years (median 58.7) were recruited from January 2001 to December 2014. [ESTRO35 2016, abstract EP 1317]

The researchers reported a 5-year OS of 88.4 percent, and a DFS of 76.1 percent. It was also noted that the DFS for histology type 1 versus 2 (p=0.005), 1-2 vs 3 (p=0.03), and stage I-II vs III-IV (p=0.04) was highly significant. Addition of external beam radiation therapy (ERBT) and vaginal brachytherapy (VB) also had a significant effect on DFS (p=0.02).
Of the 155 patients recruited 92.2 percent underwent total abdominal hysterectomy (removal of uterus through the lower abdomen) plus bilateral salpingo-oopherectomy (removal of uterus plus both ovaries and fallopian tubes). Lymphadenectomy (surgical removal of one or more groups of lymph nodes) was performed in 23 patients.

Type I EC was most common and seen in 134 patients. Low-grade G1-2 EC was seen in 77.4 percent of the patients. Median follow-up was 72 months. Regional recurrence was seen in 10 patients, and 12 patients experienced metastasis.

EC (also referred to as uterine cancer) is characterized by an uncontrolled growth of cells in the inner lining of the uterus. As per the SEER database, 60,050 new cases of EC were diagnosed in 2016 in US alone, with an estimated 635,437 women living with this cancer in 2013. OS was reported to be 81.7 percent. [SEER database. Available at http://seer.cancer.gov/statfacts/html/corp.html. Accessed on 5 May 2016]

The UK Cancer Research Centre reported 9,022 new cases of EC in 2013, with an OS of 78 percent. [Cancer Research UK. Available at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer. Accessed on 5 May 2016]

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Managing dengue fever in primary care

Dengue fever is caused by the dengue virus and borne by the *Aedes* mosquito. The disease is now endemic in over 100 countries, according to the World Health Organization, but is still most common in Southeast Asia and countries in the Western Pacific. The virus causes flu-like symptoms that generally resolve on their own with supportive care but severe cases require further management and possibly hospitalization. Primary care doctors are frequently the first point of contact for people with dengue fever. Radha Chitale spoke with Dr. Jenny Low, a senior consultant in the Department of Infectious Diseases at Singapore General Hospital, about what they can do for affected patients.

Dengue fever is a mosquito borne infection caused by the dengue virus, the most common mosquito borne viral infection in the world. We no longer talk about dengue as a disease affecting Asian countries – at least half of the world population is at risk for dengue because of where they live and their exposure to the virus from mosquito bites.

Since 2013, the total number of dengue cases recorded in Singapore has remained high at more than 10,000 cases annually. This is likely the result of a combination of factors such as high mosquito population, warmer weather, increasing urban density and low herd immunity in the Singapore local resident population.

Primary care doctors probably play the biggest role in identifying and caring for patients with dengue fever. Most of the time patients will go to their family doctor to seek medical advice first, as the symptoms of early dengue infection cannot be differentiated from other viral illnesses. If dengue is suspected, nonsteroidal anti-inflammatory drugs (NSAIDs) and intramuscular injections should be avoided due to the risk of bleeding. The family physician should monitor the patient regularly throughout the course of illness. If the doctor is concerned that the patient may be at risk for severe dengue, the doctor should then refer the patient to hospital for further medical evaluation.

Dengue fever: running the course

Dengue fever is a self-limiting illness. Once a person is bitten by a virus-carrying mosquito
he/she will come down with flu-like symptoms after an incubation period of 3-7 days. The patient may experience high fever, body aches and pains, loss of appetite and, in some cases, nausea and vomiting. Most patients will recover from the infection after about a week of illness.

One of the hallmarks of dengue fever occurs around day 4-5 of illness – the fever begins to improve but the blood platelet count starts to fall. This might cause patients to present with petechial rashes, which are small capillary bleeds just under the skin that look like small red dots. They are harmless but can be alarming and usually send patients back to the doctor who, under suspicion of dengue fever, would refer the patient to a hospital or polyclinic for a blood test.

Depending on how low the platelet levels are, and if the patient is otherwise well (if young, healthy, and able to drink sufficient fluids), he/she can be sent home and instructed to rest. Polyclinic doctors can continue to monitor the patient without referring to a hospital.

However, if the platelets are low and the patient is unwell, has poor appetite, is not able to drink sufficient fluids, or if there is a worry of dengue complications that may result in severe dengue, doctors may refer the patient to hospital for further management.

**Plasma leaks and bleeding**

The most important thing about dengue virus is its ability to cause severe disease. It is not well understood how the virus interacts with the cell lining of blood vessels but in severe dengue, plasma leaks into the surrounding tissues and accumulates. Fluid can accumulate in the lungs as well, resulting in hypotension and shock if the person does not receive fluid resuscitation in time.

The other feared complication is bleeding. Bleeding can occur in the gut, gums, urinary tract and brain. Women may also experience heavy menstrual bleeds.

Patients over 65 years, those with other medical conditions such as diabetes, pregnant women, and young children may be at risk for more severe forms of dengue infection. However, who is at risk for bleeding is not well understood.

Some other clues that a patient might be experiencing severe dengue include restlessness, abdominal pain, persistent vomiting, and bleeding of the gums or blood in the vomitus or stool. These are important symptoms for a primary care doctor to look out for to decide if a patient can be sent home to rest or come to hospital attention. If in doubt, medical practitioners should refer the patient to the hospital for further assessment.

**No “magic bullet” for dengue**

There is no curative treatment for dengue infection. Rather, medications are given to alle-
violate the signs and symptoms. Aspirin should not be given to patients. It can cause severe bleeding. Paracetamol are usually prescribed to relieve fever, muscle and joint aches, and headache. Bed rest is essential and the patient should consume plenty of water which will help to alleviate the illness.

In general, dengue fever is self-limiting. Death rarely occurs in severe cases and most well developed countries have trained medical personnel and proper care facilities to manage severe disease. The fatality rate is less than 1 percent in such countries.

Theoretically, a person may contract dengue fever four times as there are four different serotypes of virus. It is not uncommon to get dengue fever at least twice in a lifetime for people living in endemic areas. However, patients cannot fall ill with the same serotype twice as they will have developed antibodies against that serotype.

Evaluation of the usefulness of the Sanofi Pasteur dengue vaccine is ongoing. It is currently not approved for use in Singapore. The vaccine was found to be safe and among individuals aged 9 years and older, efficacy was higher than in younger children with an overall efficacy against any of the four serotypes of 60 percent.

Conclusion

Dengue fever is the most common mosquito borne viral infection worldwide. Most of the time, it is a self-limiting illness though its presentation cannot be differentiated from other viral illnesses. Severe dengue can occur in a subgroup of patients at high risk and is characterized by plasma leakage and/or bleeding. It is important to recognize the symptoms of severe disease early so that patients can be referred for proper medical care at the critical stages of illness to prevent complications and death.

Dr. Jenny Low
Senior Consultant
Department of Infectious Diseases
Singapore General Hospital

Online Resources
World Health Organization
www.who.int/topics/dengue/en
DengueNet
http://apps.who.int/globalatlas/default.asp
Singapore Dengue Infectious Disease Bulletin
www.dengue.gov.sg
US Centers for Disease Control and Prevention
www.cdc.gov/dengue
Rice-fed infants at risk for high levels of urinary arsenic

RADHA CHITALE

Infants who ate rice and rice products had higher levels of arsenic in their urine compared with infants who did not eat rice, which researchers said highlighted the need for strategies to limit children’s arsenic exposure.

“According to the European Food Safety Authority [Panel], young children [under 3 years] consume 2-3 times the amount of arsenic from food for their body weight as adults,” said Dr. Margaret R. Karagas of the Geisel School of Medicine at Dartmouth College in Lebanon, New Hampshire, US. “We really need to understand the health impacts of these levels of exposure.”

Karagas noted a growing body of evidence suggesting that in utero and early life exposure to even low levels of carcinogenic arsenic impacts on infant growth, immunity, and neurodevelopment as well as lifelong health consequences.

She and her colleagues set out to describe how often infants ate rice and rice-containing products in their first year of life and track urinary arsenic to see if there was an association. [JAMA Pediatr 2016;doi:10.1001/jamapediatrics.2016.0120]

Using data from 759 infants born between 2011 and 2014 from a US-based birth cohort study, the researchers collected dietary information every 4 months, including eating habits and when solid food was introduced.

At 12 months, the researchers also examined a 3-day food diary, which included information on whether the children ate rice cereal, white or brown rice, rice-based snacks (e.g., rice cakes, breakfast cereal), or foods sweetened with brown rice syrup. They also collected 129 urine samples at 12 months for analysis.

Most infants (80 percent) began eating rice within their first year of life, with 64 percent beginning between 4-6 months.

At 12 months, food diary data reported 43 percent of children ate something with rice in it in the past week. Thirteen and 10 percent of children at white or brown rice, respectively, an average of 1-2 times per week. Children at rice-based products or sweetened with rice syrup in the past week an average of 5-6 servings per week. In the two days preceding urine collection, 32.6 percent of children ate rice snacks, many of which were specifically targeted for consumption by infants and toddlers.

Urinalysis showed higher concentrations of
arsenic in infants who ate rice cereal (9.53 μg/L) and rice snacks (4.97 μg/L) compared with infants who ate no rice or rice products (2.85 μg/L; \( p<0.01 \) for both).

The World Health Organization and the United Nations allow for no more than 200 ng/g arsenic in polished white rice. The European Union and proposed regulation from the US Food and Drug Administration limit arsenic in infant rice products to 100 ng/g.

However, the researchers found that infant rice snacks contained 36-568 ng/g of organic arsenic and 5-201 ng/g of the more toxic inorganic arsenic.

The findings may not be generalisable as the researchers examined a population where the likely source of arsenic was dietary rather than from a water supply from which arsenic – usually inorganic arsenic – contaminates drinking water, cooking water, or crop water, for example.

“[But] children appear to be far more sensitive to the potential carcinogenic effects of arsenic and have a heightened risk for adverse [outcomes],” the researchers said. “Regulation could reduce arsenic exposure during this critical phase of development.”

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Telephone CPR improves cardiac arrest outcomes

RADHA CHITALE

A program to better equip emergency dispatchers to identify cases of community-reported out-of-hospital cardiac arrest (OHCA) and begin instructing bystanders how to perform cardiopulmonary resuscitation (CPR) by telephone resulted in quicker CPR initiation and improved outcomes for patients.

“Implementing a bundled approach to telecommunicator CPR, we were able to improve the proportion of patients who received telecommunicator CPR instructions, the proportion of patients that received any bystander CPR, and get CPR started earlier for those patients,” said lead researcher Dr. Bentley J. Bobrow, of the Arizona Department of Health Services in Phoenix, Arizona, US, where the study was concentrated.

“Most importantly, this was associated with a significant 32 percent improvement in survival to hospital discharge and improvement in functional outcome.”

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OHCA survival rates can vary significantly – from 2 to 40 percent, depending on the type of cardiac arrest – and speed is a critical factor for improved outcomes when initiating care. However, in spite of access to emergency personnel via phone (‘9-1-1’ in the US), bystander involvement in a “community” event like an OHCA remains low, at about 30 percent for bystander-initiated CPR, for example. [JAMA Cardiol 2016;doi:10.1001/jamacardio.2016.0251]

Bobrow and colleagues proposed a guideline-based telecommunicator programme in which emergency call takers and dispatchers were trained to identify early arrest and gasping breathing. If they asked and determined that the patient was neither conscious nor breathing normally, telecommunicators were to issue “prompt, assertive, and continuous” CPR instructions for a community member to follow.

For arrests of presumed cardiac origin, telecommunicators would instruct how to do compressions only, but rescue breaths were added for all other types of arrests.

This protocol was coupled with data collection, including emergency call auditing that was linked to emergency medical services and hospital outcome data, and feedback for telecommunicators.

The study itself was a prospective observational analysis tracking adult OHCA (n= 2,334) over 3 years in the Phoenix area, which included about 4 million residents. [JAMA Cardiology 2016;doi:10.1001/jamacardio.2016.0251]

Telephone CPR rates improved from 44 to 53 percent during the study duration and time to first bystander chest compression decreased from 256 to 212 seconds. Survival increased from 9 to 12 percent (p=0.045), as did favourable functional outcome (from 5.6 percent to 8.3 percent, p=0.03).

“These results suggest that the TCPR bundle, deliberately implemented and measured as part of a system-wide public health intervention, was an effective method to increase BCPR rates and survival on a large scale,” the researchers said. “This observation is a key finding because most previous work evaluating the effect of TCPR has been done in high-performance systems in the setting of strict research randomization protocols, where the investigators were closely linked to the functioning of the local systems.”

The results are important, the researchers said, because prior studies have demonstrated the benefits of telephone CPR but in a setting with more oversight “where investigators were closely linked to the functioning of the local systems.”

The researchers suggested their current findings have broader relevance in real world EMS systems and emergency centres that adopt their protocol could improve their bystander CPR and OHCA survival rates.

However, the association between improved telephone CPR and OHCA outcomes may not be so linear, Dr. James Neimann and Dr. Roger Lewis of the University of California, Los Angeles David Geffen School of Medicine in Los Angeles, California, US noted in an accompanying commentary, since the sequence of events in OHCA, where intervention begins before heart rhythm is assessed, can bias the estimation of
treatment effects within subgroups. [JAMA Cardio 2016;doi:10.1001/jamacardio.2016.0251]

In addition, they said racial and ethnic disparities exist when it comes to community-administered CPR and OHCA outcomes and rejected Bobrow and colleagues’ notion that the findings are generalizable to other settings.

“In our opinion, the completeness of success in other metropolitan areas will depend on the racial and ethnic diversity of the population and the ability of the system to accommodate the population it serves.”

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**Watercress extract clears carcinogens from cigarette smoke**

PEARL TOH

Watercress extract inhibited the activation of tobacco-specific lung carcinogen, known as nicotine-derived nitrosamine ketone (NNK) and enhanced the deactivation of other toxicants found in cigarette smoke, according to a study presented recently at the American Association for Cancer Research (AACR) Annual Meeting in New Orleans, Louisiana, US.

“The take home message is that certain dietary constituents such as isothiocyanates (ITC), which include 2-phenethyl isothiocyanate (PEITC) and sulforaphane present in cruciferous vegetables, are biologically active in modulating the enzymes that participate in the detoxification of environmental carcinogens,” said lead author Dr. Yuan Jian-Min, associate director for Cancer Prevention and Population Sciences at the University of Pittsburgh Cancer Institute (UPCI) in Pittsburgh, Pennsylvania, US.

Watercress extract, which contains 10 mg PEITC, dissolved in olive oil and taken orally four times daily for a week reduced NNK activation in smokers by 7.7 percent (p=0.023) and increased detoxification of other cigarette carcinogens such as benzene by 24.6 percent (p=0.002) and acrolein by 15.1 percent (p=0.005), but did not significantly affect crotonaldehyde (p=0.148). [AACR 2016, abstract 4347]

Participants lacking two glutathione s-transferase (GST) genes – GST mu 1 (GSTM1) and GST theta 1 (GSTT1) – benefitted even more from taking watercress extract, which significantly reduced the activation of NNK (-15.6 percent; p=0.039) and increased the detoxification of benzene (95.4 percent; p<0.001), acrolein
(32.7 percent; p=0.034), and crotonaldehyde (29.8 percent; p=0.006), compared with participants with both GST genes.

About 20-25 percent of Asians lack both GSTM1 and GSTT1 genes, while the prevalence in Caucasians is 10 percent, according to Yuan.

The phase II crossover trial randomized 82 smokers to either the PEITC-placebo or placebo-PEITC arm. In the PEITC-placebo arm, participants took PEITC 10 mg 4 times daily for one week during the treatment period, followed by a 1-week washout period before another week of placebo period. Three 24-hour urine samples collected during each of the two treatment periods were analysed for carcinogenic metabolites.

“Forty milligrams of PEITC is equivalent to the consumption of 6 ounces (170 g) [of watercress]. It is doable but certainly not in a daily routine for such consumption,” said Yuan, noting that simply eating cruciferous vegetables such as chinese long cabbage and chinese mustard (kai choi), which contain low levels of precursors PEITC, was unlikely to yield effects that were as pronounced as taking the extract.

Although quitting smoking would be a more effective way to avoid exposure to carcinogens, Yuan said quitting could take time and multiple relapses as nicotine is very addictive. And some environmental carcinogens, such as benzene, which is a natural constituent in petroleum crude oil and diesel exhaust, are unavoidable.

“Having a tolerable, nontoxic treatment like watercress extract that can protect smokers against cancer would be an incredibly valuable tool in our cancer-fighting arsenal.”

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Maternal vaccination prevents influenza in infants

ROSHINI CLAIRE ANTHONY

Infants born to women who received the influenza vaccine during pregnancy have a lower risk of developing influenza, according to a recent study.

Infants (<6 months) who were born to women vaccinated with the influenza vaccine during pregnancy had a 64 percent lower risk of one or more incidences of influenza-like illness (ILI; relative risk [RR], 0.36, 95 percent confidence interval [CI], 0.26-0.52; p<0.001). They also had a 70 percent lower risk of laboratory-confirmed
influenza (RR, 0.30, 95 percent CI, 0.19-0.46; p<0.001) and an 81 percent lower risk of hospitalization due to laboratory-confirmed influenza (RR, 0.19, 95 percent CI, 0.06-0.60; p=0.005). [Pediatrics 2016;137:e20152360]

“Our study strengthens the evidence that maternal immunization provides passive protection against influenza to infants before they are old enough to receive active immunization,” said the study authors.

The incidence of respiratory syncytial virus (RSV) infection was similar in infants born to vaccinated and unvaccinated mothers (2.1 vs 2.2 percent; RR, 0.97, 95 percent CI, 0.88-1.06; p=0.453).

Participants were 245,386 women who delivered between December 2005 and March 2014 at the Intermountain Healthcare Facilities in Utah and Idaho, US and their infants (n=249,387). Ten percent (n=23,383) of pregnant women reported receiving an influenza immunization.

Of the 866 infants who reported ≥1 incidences of ILI within 6 months postdelivery, 834 were born to unvaccinated mothers, as were 638 of the 658 infants who had laboratory-confirmed influenza.

According to the authors, women with underlying medical conditions were more likely to be vaccinated. “These women may have been recognized as high risk for influenza complications by their providers and therefore been encouraged to receive the vaccine,” they said. The occurrence of the H1N1 pandemic also appeared to increase vaccination rates in pregnant women, from 2.2 percent pre-pandemic to 21 percent post-pandemic (p<0.001).

According to study author Assistant Professor Julie Shakib, University of Utah, Salt Lake City, Utah, US, the mechanism behind this protective effect of maternal immunization is that women who are vaccinated during pregnancy pass the antibodies to their infants via the placenta.

“Since children younger than 6 months are too young to be vaccinated, the best way to protect the youngest infants before they are old enough to be immunized is to ensure pregnant women receive the influenza vaccine during pregnancy. I recommend that all clinicians who provide obstetric care advise their patients to receive the influenza vaccine and have the resources in their practices to provide the influenza vaccine to all of their pregnant patients,” said Shakib.

“Because the influenza vaccine is universally recommended, women should get the vaccine as soon as it becomes available. Because pregnant women are at high risk for serious complications themselves, it is particularly important that they receive the influenza vaccine as soon as it becomes available,” said Shakib.

“The safety and efficacy of influenza vaccine in protecting both pregnant women and infants are well-established. Future studies could and should focus on potential ways to improve the benefits of maternal vaccination in protecting young infants against influenza, such as breast feeding following maternal influenza immunization,” she said.

Attempts at directly vaccinating infants against influenza have been unsuccessful;
studies have demonstrated low seroresponse rates in infants vaccinated with the trivalent inactivated influenza vaccine. [Paediatr Infect Dis J 2009;28:1099-1104; J Infect Dis 2008; 197:1448-1454] However, other studies have also shown a reduced incidence of influenza and influenza-related hospitalization in infants (up to 6 months of age) whose mothers were vaccinated while pregnant. [N Engl J Med 2008;359:1555-1564; Arch Pediatr Adolesc Med 2011;165:104-111; Am J Obstet Gynecol 2011;204:S141-S148]

Blood cultures prior to antibiotic prescription not routine practice in the ED

ROSHINI CLAIRE ANTHONY

Broad spectrum parenteral antibiotics are commonly prescribed to patients presenting at the emergency department (ED), though often without prior blood culture sampling, according to results of a recent UK study.

In this single-centre study, researchers found that of the 72,939 patients who presented at the ED, 4,562 (6.3 percent) were administered at least one parenteral antibiotic within 48 hours of attendance. Of these, 73.3 percent (n=3,347) did not undergo blood culture sampling beforehand. Another 1,300 patients underwent blood culture sampling but were not prescribed an antibiotic. [BMC Infect Dis 2016;doi:10.1186/s12879-016-1515-1]

Of the 19,034 patients who were hospitalized after ED presentation, 12.4 percent (n=2,365) underwent blood culture sampling, while 22.9 percent (n=4,357) were prescribed a parenteral antibiotic.

“At all ages, the use of parenteral antibiotics far exceeded the use of blood cultures,” said the authors, referring to the higher use of cultures and antibiotics in individuals aged ≥30 years, and the sharp increase in use in the elderly (age ≥60 years in men and ≥70 years in women).

According to Dr. Laura Shallcross, a clinical lecturer at the University College London (UCL) Centre for Infectious Diseases Informatics, London, UK and one of the study authors, national
guidance in England recommends that cultures (not restricted to blood) should be taken before antibiotics are initiated (exceptions are made in the incidence of severe sepsis or life-threatening infections). [Start Smart then Focus; available at https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus, accessed 5/5/16]

However, regular use of blood cultures does have drawbacks. “For less severe infections where bacteraemia is unlikely, increasing the use of cultures may result in unnecessary healthcare expenditure with little diagnostic yield,” said Shallcross. “In theory, taking a blood culture might help to reduce the inappropriate use of antibiotics, if a negative culture led to a decision to stop antibiotics. The problem with this approach is that blood cultures lack the predictive power to reliably rule out bacterial infection, underscoring the need for new approaches to guide prescribing decisions in the ED,” she said.

“We need large observational studies to understand more about the use of antibiotics in secondary care for different clinical syndromes, and how this relates to microbiological and clinical data. This would inform the development of interventional studies to reduce inappropriate prescribing in secondary care,” said Shallcross.

To investigate the frequency of blood culture usage when parenteral antibiotics are introduced in the ED, researchers obtained electronic health records of patients who presented at the University Hospital Birmingham ED in 2014. Inclusion criteria were electronic requests for blood culture sampling and antibiotic prescription within 48 hours of presentation at the ED.

The most commonly prescribed antibiotics were co-amoxiclav (29.9 percent), piperacillin-tazobactam (20 percent), flucloxacillin (16 percent), clarithromycin (8.2 percent), and meropenem (one in 20 patients). An organism was detected in almost 12 percent of patients (n=282) who underwent blood culture sampling, with Escherichia coli (n=78) and Staphylococcus aureus (n=21) being the main causes of bacteraemia.

“More than half of the antibiotics prescribed to patients in this study were broad spectrum, despite increasing evidence that broad spectrum prescribing is associated with antimicrobial resistance bacteria,” said the authors, who expressed their concerns that as most patients who are hospitalized first present at the ED, prescribing practice in the ED could set up the pattern of antimicrobial use in the hospital.
Vitamin D deficiency high in children with type 1 diabetes, healthy weight Caucasian children at greater risk

KAVITHA G. SHEKAR

Children and adolescents with type 1 diabetes mellitus (T1DM) have low levels of vitamin D (25-hydroxyvitamin D), a key component for the development of healthy bones, cardiovascular health, good immune system, and glucose metabolism, say researchers.

“To our knowledge this is the first study that has been adequately powered to examine the association between 25-hydroxyvitamin D and HbA1c [a measure of diabetes control] in children and adolescents with type 1 diabetes,” said lead author Professor Terri H. Lipman from the University of Pennsylvania School of Nursing, Philadelphia, Pennsylvania, US.

About 90 percent of the participants had 25-hydroxyvitamin D levels ≤75 nmol/L. Vitamin D deficiency (25-hydroxyvitamin D levels ≤50 nmol/L) was observed in 40.6 percent of the participants. Vitamin D insufficiency (25-hydroxyvitamin D levels between 51-75 nmol/L) was observed in 49.2 percent of the participants. [Diabetes Res Clin Pr 2016;115:54–59]

The mean HbA1c was 8.6±1.4 percent and mean 25-hydroxyvitamin D levels were found to be 54.6±17.8 nmol/L.

Vitamin D levels were also significantly lower in 13 to 18 year old females, and those receiving treatment with multiple insulin injections.

Lipman and team compared the results of this study to previous national health and nutrition examination surveys (NHANES). While the vitamin D deficiency was higher in the study group compared to the 2005-2006 NHANES database, vitamin D insufficiency was comparable to that reported in the 2001-2006 NHANES study for healthy 6 to 11 year old children and the 2005-2006 NHANES results for healthy children and adolescents aged 1 to 18 years.

They also found that the percentage of participants of healthy weight with vitamin D deficiency in their study was twice the number reported in the 2005-2006 NHANES report (44 versus 20.1 percent, respectively). The deficiency was however similar in obese individuals (38.5 vs 36.8 percent, respectively).

Another striking result was the increase in incidence of vitamin D deficiency in Caucasian children compared to the 2005-2006 NHANES survey results (88 vs 58.9 percent), while num-
bers remained comparable in African American children (97 vs 94 percent).

“These additional findings challenge the common perceptions that only obese, African American children and adolescents have the highest risk of presenting with low levels of 25-hydroxyvitamin D,” said Lipman. “As this study confirms, there may be an alarmingly high prevalence of 25-hydroxyvitamin D levels ≤50 nmol/L in healthy weight, Caucasian children and adolescents with T1DM that should not be dismissed.”

The study participants were 197 children and adolescents aged 7 to 18 years with T1DM for ≥1 year. Those with a history of smoking, HbA1C >12 percent, ketoacidosis, inflammatory disorder, abnormal complete blood count, hepatic or renal dysfunction, cancer, malabsorption, on oral corticosteroid, anti-inflammatory or immunosuppressive drugs, metformin, angiotensin-converting enzyme inhibitors, and/or aspirin were excluded from the study.

The researchers obtained non-fasting blood samples and used the serum to measure both blood glucose and 25-hydroxyvitamin D levels.

“The findings of this study underline the importance of vitamin D screening in all children and adolescents with T1DM,” said Lipman.