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CONTINUING MEDICAL EDUCATION

The Role of the GP in Managing Female Infertility

GPs often provide the first medical consultation for an infertile couple and can provide basic advice and education regarding fertility and conception.

IN THE MEDICINE

Hepatitis C Virus Infection Screening in Adults

The Agency for Healthcare Research and Quality (AHRQ) provided support to the Oregon Evidence-Based Practice Center to perform a systematic review to evaluate the evidence about the effects of screening for Hepatitis C Virus (HCV).

JOURNAL DIGESTS FROM REUTERS HEALTH

Consumer Reports Advises Pregnant Women to Avoid Tuna

Aspirin, take two: Research identifies a second effect of the drug against inflammation

Blood pressure medication does not cause more falls

CME Answers for the month of August 2014

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The latest medical news from the leader supplier.

CME - Continuing Medical Education
Alleviating Allergic Rhinoconjunctivitis
A Task For All Seasons
Allergic rhinoconjunctivitis is common, impacts significantly on the quality of life of the sufferer and is responsible for an enormous economic burden. Symptoms may occur all year round or seasonally, or have seasonal flares depending on the allergen causing the symptoms.

In the Medicine
Treatment for Depression After Unsatisfactory Response to SSRIs in Adults and Adolescents
Although patients with MDD have a 63-percent response rate during 6 to 12 weeks of treatment with second-generation antidepressants, 53 percent do not achieve remission.

Notes: The above articles are subject to change without prior notice.

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CONTINUING MEDICAL EDUCATION

Managing Cough in Adults
Is there a serious underlying cause?
A thorough history and physical examination, as well as targeted investigations, adequate treatment trials and the option of combining therapeutic approaches are important components of an effective management plan in patients with acute and chronic cough. Serious underlying causes such as malignancy, pneumonia or congestive cardiac failure should be excluded.

IN THE MEDICINE

Methods Effectiveness of Insulin Delivery and Glucose Monitoring in Diabetes Mellitus
Diabetes mellitus is a group of metabolic diseases resulting from defects in insulin secretion from the pancreatic beta-cells, resistance to insulin action at the tissue level, or both. The resultant hyperglycemia, if untreated, can lead to long-term complications, including microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary heart disease and cerebrovascular disease).
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NEWBORNS OF HEAVY MOTHERS AT RISK FOR BREATHING PROBLEMS

NEW YORK (Reuters Health) - Babies of overweight and obese mothers are more likely to have oxygen-deprivation problems at birth, according to a new study.

The heavier a woman is, the greater the risks to her newborn, researchers found.

“Maternal obesity is associated with a number of complications during pregnancy and delivery, but the underlying mechanism is not fully understood,” said Dr. Marie Blomberg of Linkoping University in Sweden. She was not involved in the new study.

To learn more, researchers analyzed data from a medical register of all live singleton, term births between 1992 and 2010 in Sweden, which included more than 1.7 million babies.

The register had information on women’s height and weight early in pregnancy, as well as babies’ medical problems and so-called Apgar scores.

The Apgar score assesses vitality using measures of heart rate, breathing, muscle tone, skin color and activity on a scale from zero to 10. There can be many reasons for a low Apgar score, but the most common reason is lack of oxygen, lead author Dr. Martina Persson told Reuters Health in an email.

Persson worked on the study at the Karolinska Institutet in Stockholm.

Less than one in 1,000 babies had an Apgar score between zero and 3 at five minutes after birth, and even fewer had that low a score at 10 minutes after birth.

Compared to babies of normal-weight mothers, babies with overweight mothers were 32 percent more likely to have an Apgar score that low at 10 minutes.

Babies of obese mothers were 57 percent more likely to have a low Apgar score, and those of severely obese mothers were 80 percent more likely.

A newborn’s risk of seizures also increased with maternal weight. For instance, babies of severely obese mothers were twice as likely to have a seizure as those of mothers with a healthy weight.

The increased risks were similar for meconium aspiration, which happens when the baby releases stool in the womb and inhales the stool-tainted amniotic fluid.

“Meconium release is a sign of fetal stress,” Persson said. “Meconium aspiration may give severe breathing problems in the newborn and is associated with birth asphyxia and low Apgar scores.”
“Meconium aspiration and seizures could be serious in the immediate newborn period although still the majority of these children will be healthy,” Blomberg told Reuters Health in an email.

Researchers don’t know why these risks, which all relate to lack of oxygen, go up for babies of overweight and obese women, Persson said.

Obesity in pregnant women has been associated with metabolic changes and inflammation, which could affect the placenta and fetal environment in a way that leads to low oxygen levels and more fetal growth, she noted.

Also, larger babies, often born to larger mothers, may be more likely to experience trauma during delivery, which could result in lack of oxygen, she said.

“One must bear in mind that even though these conditions are potentially very dangerous for the baby, the absolute risks for the studied outcomes are low,” Persson said.

Even with the most obese mothers, the risk of infants having a low Apgar score at five minutes was still only 0.24 percent, or less than three babies out of every 1,000.

In addition to encouraging prospective mothers to strive for a healthy weight, doctors can closely monitor babies during labor and delivery, which likely reduces the risk of lack of oxygen at birth, she said.

“Enjoy your pregnancy!” Persson said. “Try to eat healthy and be physically active. Seek support from your midwife in order to change bad eating habits and try not to gain too much weight during pregnancy.”

By Kathryn Doyle

**FASTER VACCINATION SAVES LIVES, MONEY DURING FLU PANDEMIC**

NEW YORK (Reuters Health) - Shortening the time between the start of a severe flu outbreak and mass vaccination saves lives and money, suggests new research.

Traditional methods, such as washing hands and wearing face masks, are also effective at controlling an outbreak until vaccines are made available, researchers said.

“We saw what happened in 2009 and we wanted to take a look at if the response was similar to that in a more severe pandemic episode how prepared are we,” said Dr. Nayer Khazeni, the study’s lead author from the Stanford University School of Medicine in California.

The World Health Organization declared in June 2009 that an outbreak of the H1N1 influenza virus qualified as a pandemic, which is when a virus circulates around the globe and most people do not have immunity against it. The strain was referred to as “swine flu” early on.

Khazeni and her fellow researchers write in the Annals of Internal Medicine that vaccination against H1N1 did not start until about nine months after the outbreak began.
In a previous study, they found that every four-week delay in vaccinations during that outbreak led to significant increases in infections, deaths and costs.

The researchers used a computer model for the new study to estimate what those figures might look like in a city like New York during a more severe flu pandemic, depending on when the first 30 percent of the population became vaccinated.

The pandemic used for the computer model was crafted like the 1918 Spanish flu pandemic, which killed an estimated 30 to 50 million people globally, including 675,000 in the U.S.

The flu virus used in the model also borrowed traits from two emerging bird flu viruses from Asia and the Middle East, H7N9 and H5N1.

The researchers estimated that each person with the flu would infect about two more.

About 48,250 people would die if it took a full year from the start of the outbreak for 30 percent of a city with about 8 million people to get vaccinated, according to the model.

About 45,890 people would die if vaccination took nine months - as it did during the 2009 outbreak. Deaths would fall to about 34,480 if vaccination was pushed up to four months.

Healthcare costs would also fall by about $100 million city-wide if widespread vaccination was moved from nine months to four months, or almost $4 billion nationally.

The researchers note that the current process to create flu vaccines takes about five months under the best circumstances, however. New technology that does not use eggs to develop a vaccine may allow for shorter production times, they write.

“These figures may help policymakers decide what scenarios warrant a concerted effort between vaccine manufacturers and the government to speed production and administration,” they add.

If speeding up vaccine production is not possible, the researchers also found that non-drug techniques like wearing masks, washing hands and staying in may control the outbreak until a vaccine is ready.

“I think that’s a really encouraging finding,” Khazeni said.

Dr. Mark Mulligan, executive director of the Hope Clinic of the Emory Vaccine Center in Atlanta, told Reuters Health that people should know the best defense against the flu is prevention.

“That weapon - although not perfect - is the vaccine,” he said. “People should be vaccinated annually and when there is a pandemic we want to get as many people vaccinated as possible.”

Mulligan, who was not involved with the new study, also said it’s important that people follow the advice that’s already known, such as washing hands and coughing into the crook of the arm.

By Andrew M. Seaman
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STUDY QUESTIONS ROLE OF VITAMIN D IN ASTHMA

NEW YORK (Reuters Health) - Giving people with asthma and low vitamin D levels extra doses of the vitamin doesn’t do much to help their lungs, a new study suggests.

Previous research had linked low vitamin D levels to more asthma-related problems, like weaker lungs and more asthma exacerbations.

But it wasn’t clear if vitamin deficiencies were causing those problems, or if giving patients extra vitamin D was the answer.

Lead author Dr. Mario Castro from Washington University School of Medicine in St. Louis, Missouri, said as many as two-thirds of his asthma patients are lacking in vitamin D.

“Our thought was that vitamin D would potentially make... the standard therapy, inhaled corticosteroids, work better in these patients, and that it would reduce their asthma exacerbations,” he told Reuters Health.

To test that theory, the researchers studied just over 400 adults with asthma and low vitamin D levels. They randomly assigned half of the participants to take vitamin D3 supplements every day, and the other half to take a vitamin-free placebo pill.

All of the patients also took corticosteroids to help keep their asthma in check.

Over the next six months, Castro and his team tracked so-called treatment failures - the times patients were sent to the emergency room or hospitalized for asthma, had declines in lung function or had to increase their use of asthma medication.

They found between one-quarter and one-third of participants in both the vitamin D and placebo groups had a treatment failure during the study. The only benefit linked to vitamin D was that patients in the vitamin group needed slightly lower doses of corticosteroids to control their asthma.

When the researchers looked only at patients whose vitamin D levels significantly improved from the supplements, they found benefits in some areas compared to the placebo group - such as fewer patients with an asthma exacerbation - but not in other areas.

The findings don’t support using vitamin D as a general treatment strategy for people struggling with asthma symptoms, the authors write in the Journal of the American Medical Association. They also presented their results Sunday at the American Thoracic Society International Conference in San Diego.

Castro said he thinks it is still appropriate to treat some asthma patients with vitamin D while more research is being conducted. He prescribes it to people with low vitamin D levels who also have uncontrolled asthma symptoms, and monitors them to make sure their levels come up.

“I think there may be some benefit, and vitamin D is inexpensive and has (minimal) side effects,” he said.
Vitamin D3 supplements cost a few dollars per month for the dose used for most of the study, about 4,000 international units.

Dr. Ken Kunisaki from the University of Minnesota in Minneapolis said there are still some questions, such as what is a big enough dose of vitamin D to give people who are deficient.

But he said that in general, the new findings were "disappointing."

Regarding the role of vitamin D in asthma, "It's been a fairly consistent story from the observational studies," Kunisaki, who specializes in pulmonary and critical care medicine, told Reuters Health.

Those studies relied on measuring people's vitamin D levels and asthma symptoms, rather than instructing some patients to take extra vitamin D. In observational studies, it's possible another underlying factor could explain the link between low vitamin D and asthma-related problems, he said.

"It goes to show why we do randomized clinical trials," said Kunisaki, who wasn't involved in the new research.

"This study would say that at least in this population, there's no role for routinely looking at vitamin D levels, at least for asthma-control purposes," he concluded.

The study was funded by the National Institutes of Health, and the asthma medications used were provided free of charge by their manufacturer, Sunovion Pharmaceuticals.

By Genevra Pittman

MUSCLE PAIN NOT WELL DEFINED IN MOST STATIN STUDIES

NEW YORK (Reuters Health) - Studies evaluating cholesterol-lowering drugs might find more muscle problems if they did a better job of defining and asking about muscle pain, suggests a new review.

Researchers say 10 to 25 percent of real-world patients on statins report having muscle problems, but clinical trials consider these side effects to be rare.

"A lot of patients complain about . . . muscle aching while they're on statins," Dr. Paul D. Thompson told Reuters Health.

Thompson, who worked on the study, is chief of cardiology at Hartford Hospital in Connecticut.

"So that's why we did the study - we wanted to see, why is there such a big difference between what doctors say who practice taking care of patients and what the literature says?" he said.

To see how muscle-related side effects are evaluated and reported in trials of statins, Thompson and his colleagues searched for studies that compared people taking a statin with those taking a drug-free placebo pill for at least six months.
They found 42 studies that examined seven different types of statins, including atorvastatin (marketed as Lipitor) and simvastatin (Zocor).

Of those studies, 26 reported on muscle problems, such as muscle pain, weakness and cramps. Only one specifically asked participants if they had any muscle problems.

The researchers found the frequency of muscle aches and pains was slightly higher in the statin groups than in placebo groups: 12.7 percent compared to 12.4 percent, according to the results published in the American Heart Journal.

But they say everyday muscle aches and pains could not be distinguished from muscle pain linked to statins because most trials did not use a standard definition for statin-related muscle problems.

Thompson said his own previous study defined statin-associated muscle problems as new or increased pain, cramps or aching that is not linked to exercise and persisted for two weeks. Pain had to go away within two weeks of patients stopping a statin and come back within four weeks of them restarting the drug.

In that study, nine percent of participants using statins reported muscle aches, compared to four percent of those taking a placebo. “So we think about five percent of people really have muscle aching related to the statins,” Thompson said.

He added that pain and aches due to statins may not mean actual damage is occurring in the muscle.

“Just because (patients) have muscle aching doesn’t mean anything terrible is going on in their muscle because usually when they stop taking the drugs it goes away,” he said.

Thompson said statin-related muscle pain must be confirmed by a doctor, but patients can look out for certain signs and symptoms.

“It’s usually large muscle groups of the legs and buttock and back,” he said. “It’s not usually that your fingers hurt or something like that.”

It’s also possible that the muscle pains are more of a problem for people who are physically active.

“We’ve shown that people who exercise a lot tend to have more evidence of muscle injury - we think the cause may be related to a failure to repair damaged muscle, so if you’re damaging your muscle by exercising, maybe you don’t repair it as well,” Thompson said.

By Shereen Jegtvig

FTC COMMISSIONER WARNS ON MOBILE HEALTH-DATA GATHERING

SAN FRANCISCO (Reuters) - Federal Trade Commissioner Julie Brill, speaking in Washington on Wednesday, expressed concern about the way apps on smartphones and mobile devices are siphoning sensitive health data, and how some of that information may then be shared with third parties.
After a panel discussion hosted by U.S. political site The Hill, Brill told Reuters that many companies now prefer to focus on how data is used, because that is where "the rubber hits the road when it comes to patient harm." Developers should give consumers more tools and "robust choice mechanisms" before any sensitive data is collected and stored.

“We don’t know where that information ultimately goes,” Brill told the panel. “It makes consumers uncomfortable.” She has put pressure on Congress to pass laws prohibiting the collection of personal information under false pretenses.

The debate around the gathering of consumer data is intensifying as Silicon Valley tech companies take a more active interest in mobile health. Apple Inc and Google Inc revealed new health-focused services for apps developers in recent months, dubbed Google Fit and HealthKit.

Brill’s comments followed a May report in which the FTC revealed the results of a study of mobile health-app developers, which found that a good portion collect consumer health data and give it to third-party entities.

The study, which focused on data-sharing in relation to 12 mobile health and fitness apps, found that developers were sharing users’ information with 76 different parties, including marketers.

In an interview with Reuters, Brill stressed that “no one is talking about new regulations.”

The agency has spent years communicating best practices for the rapidly emerging mobile health industry to follow, she said. FTC commissioners have also previously stressed that health data is sensitive and requires special protections.

Brill pointed to FTC initiatives like Reclaim Your Name, which would give consumers more tools to reassert control over their health data.

Some advocacy groups, like the Association for Competitive Technology, which represents application developers, fear that innovation could be stunted if information collection were curtailed.

“The mobile health industry needs to educate the FTC about why collecting health data can provide better health outcomes,” Morgan Reed after the panel. “If we fail to do this, the commission could take action that would devastate app developers.”

At its developer conference in June in San Francisco, Apple unveiled HealthKit, which will pull data together such as blood pressure and weight now collected by healthcare apps and devices on the iPhone and iPad.

Brill declined to comment on whether the FTC is concerned about HealthKit, as the service has yet to be released to the public.

By Reuters Staff

Continued on page 31
Managing Cough in Adults
Is There a Serious Underlying Cause?

A thorough history and physical examination, as well as targeted investigations, adequate treatment trials and the option of combining therapeutic approaches are important components of an effective management plan in patients with acute and chronic cough. Serious underlying causes such as malignancy, pneumonia or congestive cardiac failure should be excluded.

Cough is a normal physiological reflex to remove secretion from and prevent inhalation of foreign material into the lungs. It is one of the most common reasons for patients to present in primary care and has significant social and economic impacts. It also affects patients’ well being and can significantly impair quality of life.1-3

IN SUMMARY

• A detailed medical history and physical examination are important in managing patients with cough.
• Acute cough is defined as cough lasting less than three weeks and chronic as lasting more than eight weeks.
• Acute cough is commonly caused by infections (especially viral) of the respiratory tract.
• It is important to exclude serious illness as a cause of acute cough and to exclude a postinfectious cause in patients with subacute cough.
• A trial of cessation of medications that can cause cough is recommended.
• Chronic cough is strongly associated with smoking. Upper airway cough syndrome, asthma or gastro-oesophageal reflux disease are the most likely causes of chronic cough in a healthy nonsmoker.
• A combined therapeutic approach in sequential steps and referral of the patient to a specialist may be required in the management of chronic cough.

BENJAMIN KWAN
MB BS, BSc(Med), FRACP

Dr Kwan is a respiratory and sleep medicine Staff Specialist and Network Director of Physician Training at St George and Sutherland Hospitals Network; and Conjoint Lecturer at The University of New South Wales.

CHIN GOH
MB BS, BSc(Med)

Dr Goh is a respiratory and sleep medicine Advanced Trainee (final year) at St George Hospital, Sydney, NSW.
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Cough can be difficult to manage and many evidence-based guidelines have been published, with the American College of Chest Physicians recommending that clinicians use an empiric, integrative diagnostic approach in adult patients presenting with cough. This article outlines a diagnostic approach to the management of cough in adults.

MECHANISM OF COUGH
The cough reflex is usually initiated by stimulation of afferent structures found in upper and lower airways, as well as the tympanic membrane and external auditory meatus. These structures respond to both chemical and mechanical stimuli and are innervated by the vagus nerve, which sends a signal to the ‘cough centre’ in the brain stem, with subsequent motor activation of expiratory muscle groups, including the diaphragm, larynx, pharynx and intercostals. However, cough can also be generated at a central nervous system level or voluntarily.

COUGH CATEGORISATION
Cough can be arbitrarily categorised by time, with acute cough typically lasting less than three weeks and chronic cough lasting more than eight weeks. Cough lasting between these periods can be defined as subacute cough and can be managed as chronic cough once postinfectious cough is excluded. Cough can also be described as productive (>30 mL of sputum per day) or nonproductive. Clinicians should also enquire about any particular trigger, as well as quantity and quality of sputum (including presence of blood) produced.

Acute cough
Recent onset cough is usually self-limiting and commonly caused by infections (especially viral) of the upper or lower respiratory tracts (common cold). It affects both healthy adults and those with chronic lung diseases. Clinically, it is important to determine through medical history and physical examination whether the acute cough is due to a nonlife-threatening diagnosis such as infection, an exacerbation of a pre-existing condition (e.g. asthma) or chronic obstructive pulmonary disease, or whether it is due to a more serious cause such as pulmonary embolism, congestive heart failure or pneumonia. Features such as coryzal symptoms, sputum and fever or physical examination findings such as upper airway inflammation and presence of crackles on auscultation may help determine the anatomical site of the infection (see the box).

GUIDELINES ON COUGH
- European Respiratory Society: ERS guidelines on the assessment of cough
- British Thoracic Society: Recommendation for the management of cough in adults
- American College of Chest Physicians: Diagnosis and management of cough executive summary

Most patients presenting with acute cough do not need any investigation. However, patients who are at risk or who present with more worrying symptoms will require a chest x-ray and other specific investigations. Although there is little evidence that various over-the-counter preparations have a specific pharmacological effect, many patients do report a clinical benefit. Dextromethorphan, menthol, sedative antihistamines, codeine and pholcodine have all been shown to suppress cough reflex in clinical studies using cough challenge methodologies. Codeine and pholcodine are opiates and have a greater side effect profile compared with dextromethorphan.

The flowchart is an example of a

IMPORTANT HISTORY AND EXAMINATION FINDINGS NOT TO BE MISSED

History
- Recent respiratory infection
- Occupational factors
- Smoking history
- Prominent dyspnoea
- Haemoptysis
- Systemic features (e.g. fever, weight loss)
- Dysphagia, aspiration, astrosophageal reflux symptoms
- Medications (e.g. angiotensin converting enzyme inhibitors)
- Prominent aggravating factor

Physical examination findings
- Crackles on auscultation
- Examination of ear, nose and throat for rhinosinusitis
- Spirometry, bronchodilator reversibility, bronchial provocation challenge
clinical pathway for managing acute cough. Some of the usual common causes of acute cough are described below.

**Acute bronchitis**
Acute infection of the larger airways in otherwise healthy patients is most often viral and does not require antibiotics. Use of a neuraminidase inhibitor such as oseltamivir within 48 hours of onset of symptoms can reduce the clinical course of an influenza infection by one day on average.13 In treating the common cold, a first-generation antihistamine together with a decongestant has been shown to reduce severity and hasten resolution of cough and postnasal drip whereas the NSAID naproxen also improves cough.12,14

The incidence of infection caused by *Bordetella pertussis* (whooping cough) in adults has increased worldwide and should be considered if the cough is persistent and paroxysmal or accompanied by post-tussive emesis or inspiratory whoop.15 Investigation should include an early posterior nasopharyngeal swab for culture and/or polymerase chain reaction testing for *B. pertussis*. Recommended treatments include isolation for five days and use of macrolide antibiotics, which can achieve clinical benefit if given within the first week whereas later treatment may minimise spread of infection.16

**Asthma and asthma-like syndromes**
Asthma onset can be late in adulthood in individuals with smoking history or preceding rhinitis.17 Patients with uncontrolled or poorly controlled asthma can present with acute cough, particularly

**Abbreviations:** ACEI = angiotensin-converting enzyme inhibitor; COPD = chronic obstructive pulmonary; GORD = gastro-oesophageal reflux disease; ICS = inhaled corticosteroids.

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### SUGGESTED MANAGEMENT PATHWAY FOR PATIENTS WITH ACUTE COUGH

<table>
<thead>
<tr>
<th>Patient presents with acute cough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take a history and perform an examination, with or without investigations (e.g. chest x-ray, spirometry)</td>
</tr>
</tbody>
</table>

**Are any of the following life-threatening conditions suspected?**
Severe asthma/COPD exacerbation, severe pneumonia, pulmonary embolism, acute heart failure, anaphylaxis, pneumothorax

**Are any of the following not-to-miss conditions suspected?**
Lung cancer, tuberculosis, recurrent aspiration, foreign body inhalation, interstitial lung disease

---

<table>
<thead>
<tr>
<th>Is it a specific acute cough syndrome?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Acute bronchitis</strong></td>
</tr>
<tr>
<td>• Treat infections</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drug-induced cough</strong></td>
</tr>
<tr>
<td>• Cease offending drug (e.g. ACEI)</td>
</tr>
<tr>
<td>• Stop smoking</td>
</tr>
</tbody>
</table>

| No |
| **Postinfective cough** |
| • Review acute bronchitis |
| • Consider Bordetella pertussis infection |

| **Asthma and asthma-like syndromes** |
| • Use ICS, bronchodilators, corticosteroids |
| • Avoid triggers |
| • Treat infections |
| • Treat comorbid conditions |

| **GORD** |
| • Acid suppressing agents |
| • Promotility agents |
| • Consider specialist review |

| **Upper airway cough syndrome** |
| • Vocal hygiene |
| • Nasal washes |
| • Antihistamines |

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Continuing medical education

after exposure to trigger factors or spontaneously at night. Associated symptoms such as chest tightness, wheeze or dyspnoea and a history of asthma or atopy are helpful. Obstructive spirometry with significant bronchodilator reversibility is a typical finding, and most patients will have a positive bronchoprovocation test.

Management of asthma includes allergen avoidance, appropriate preventive and reliever bronchodilators, and management of exacerbation according to established guidelines (e.g. the Global Initiative for Asthma guidelines). Initial treatment should include use of an inhaled corticosteroid and a β-agonist, and a response should be expected within one week. Oral leukotriene inhibitors may also be effective in people with asthma-induced cough, and can be added if cough persists.

It is important to consider a foreign body as a cause of acute cough, especially in patients at risk of aspiration. Radio-opaque objects may be visible on plain x-ray; further imaging (e.g. CT scan of the chest) or endoscopic procedures (e.g. nasoendoscopy or bronchoscopy) may be needed for diagnosis and retrieval of the foreign body.

In travellers or immigrants from countries where tuberculosis is prevalent and who present with a cough plus associated systemic features (such as weight loss, night sweats or cervical lymphadenopathy) and chest x-ray changes, Mycobacterium tuberculosis infection will need to be excluded. Early morning sputum samples should be carried out to look for acid-fast bacilli. Referral to a specialised tuberculosis chest clinic is warranted in highly suspected individuals. Further investigations such as Mantoux skin test or QuantiFeron Gold and bronchoscopic investigation may then be arranged. Another diagnosis that is important not to miss is malignancy. Suspicion should be raised in people who are heavy smokers and have alarming clinical features such as haemoptysis and weight loss (see the chronic cough section). Other rarer causes of acute cough include pneumothorax, pleural effusion, pulmonary embolism and heart failure.

Subacute cough

Currently there is little data regarding causes and treatment of subacute cough. Clinically it is useful to determine if the cough is of a postinfectious nature. In such cases, probable reasons for lingering cough include persistent upper airway irritation, mucous accumulation, persistent postnasal drip or bronchial hyper-responsiveness. It is important to exclude infections such as tuberculosis or pertussis, and acute exacerbation of chronic respiratory diseases such as asthma or COPD. In noninfectious cases of subacute cough, the recommendation is to evaluate and manage the patient as presenting with chronic cough.

Chronic cough

The prevalence of chronic cough is strongly associated with smoking, with people who are current smokers having a two- to three-fold greater prevalence compared with those who have never smoked. Environmental and occupational factors, including particulates, certain home heating components (e.g. wood stove, kerosene heater) and road traffic pollutants, may also need to be addressed. Several prospective studies have reported that the most likely causes of chronic cough in people who are nonsmokers and who have no recent chest infection and a normal chest x-ray include upper airway cough syndrome.
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³ Proportion of WOMT
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0.7 (95% CI, 0.6-0.8) for Drospirenone 24/4 vs. other OCs. Crude and adjusted HR were similar²

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The preferred term of ‘unexplained cough’ is used. No clear cause is found in up to 20% of cases in carefully investigated case series, but probably more in clinical practice.21

SUGGESTED MANAGEMENT PATHWAY FOR PATIENTS WITH ACUTE COUGH

Patient presents with chronic cough

Take a history and perform an examination, with or without investigations (e.g. chest x-ray, spirometry)

Are any alarming features present? (e.g. significant smoking history, haemoptysis, prominent dyspnoea, systemic features, complicated gastrooesophageal reflux symptoms, feeding difficulties, recurrent pneumonia)

Yes

No

Consider specialist referral for further investigations (e.g. speech pathologist review, modified barium swallow, 24-h oesophageal pH monitor, induced sputum, endoscopy, sinus imaging, polysomnography, high-resolution CT, bronchoscopy, echocardiography)

Is a specific chronic cough syndrome present?

Yes

No

Upper airway disease*

• Nasal washes
• Nasal corticosteroids
• Antibiotics
• Antihistamines
• Allergen avoidance
• Immunotherapy

Vocal cord dysfunction

• Speech pathology review: vocal cord training
• Optimise comorbidities

Obstructive sleep apnoea

• Weight loss
• CPAP
• MAS
• Optimise comorbidities

GORD

• Chronic PPI use
• Per acute management

Chronic lung diseases†

• Treat underlying lung disease
• Consider specialist input

Nonasthmatic eosinophilic bronchitis

• Inhaled corticosteroids

Consider nonspecific cough syndrome or ‘unexplained cough’

• Empirical treatment: PPI, inhaled corticosteroids and speech pathologist review
• Respiratory specialist centre referral

ABBREVIATIONS: CPAP = continuous positive airway pressure;
GORD = gastro-oesophageal reflux disease;
MAS = mandibular advancement splint;
PPI = proton pump inhibitors.

* Upper airway diseases include allergic rhinitis, chronic rhinosinusitis.
† Chronic lung diseases include airway abnormalities (e.g. bronchomalacia), asthma, bronchiectasis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis.
In managing a patient with chronic cough in primary practice, it is important to take a detailed history, including current and previous occupation, domestic environment, dust/chemical exposure and presence of pets, and perform a physical examination. A chest x-ray and spirometry should also be performed. If an obstructive pattern is observed, a pre- and post-short-acting β₂-agonist effect on forced expiratory volume in 1 second (FEV₁) should be measured.

There is currently no evidence linking the cough duration to a particular cause, nor ongoing viral infection to persistent cough. There is also a poor diagnostic sensitivity and specificity relating to cough characteristics. However, cough reflex sensitivity may be enhanced by viral infection, ACE inhibitors, GORD and asthma. Any associated alarming features warrant immediate attention. These features include a significant smoking history (more than 20 pack years), haemoptysis, new onset hoarseness, prominent dyspnoea (nocturnal or resting), systemic features (e.g. fever, weight loss, night sweats), complicated gastro-oesophageal symptoms (e.g. anaemia, overt bleeding, dysphagia), feeding troubles or recurrent pneumonia. Abnormal respiratory clinical findings or radiographic changes also merit further investigation.

Systematically addressing the following specific common conditions may aid in the management of chronic cough. However, if there is failure of empirical treatment or targeted investigations are normal, the patient should be referred to a specialist. An approach to the diagnosis and management of chronic cough is shown in the flowchart.

**Upper airways disease**
Clinical features of nasal inflammation (blockage, rhinorrhoea, itchiness) with conjunctivitis may suggest allergic rhinitis, especially in atopic individuals. Skin prick testing may assist in identifying common allergens. Treatment of cough in this setting involves management of allergic rhinitis according to current guidelines, primarily with topical nasal corticosteroids. Antihistamines, decongestants, allergen avoidance and immunotherapy may also play a role.

Patients with chronic rhinosinusitis who experience mucopurulent nasal discharge, sinus pain, anosmia and headaches may also be burdened by chronic cough. Management includes nasal saline irrigation, intranasal corticosteroid therapy for at least four weeks, with oral antibiotics cover for the same period. Use of oral corticosteroids for a short duration is indicated if there is associated nasal polyposis. If the above medical therapy fails, a CT scan of the sinuses should be arranged for diagnosis and/or surgical planning, with subsequent referral of the patient to an ear, nose and throat specialist.

**Vocal cord dysfunction**
Patients with vocal cord dysfunction experience stridor and dysphonia due to episodic, uncontrollable narrowing of the cords during inspiration, with associated dyspnoea and cough occasionally. Direct laryngoscopy and flattening of the inspiratory flow–volume loop on spirometry can support the diagnosis. Acute interventions of vocal cord paradoxical movement sometimes involve continuous positive airway pressure and, rarely, tracheostomy. Successful longer-term treatment reported involves voice therapy and psychological counselling. Apart from reassurance, irritant avoidance and supportive care, these patients are perhaps best managed in consultation with an experienced speech pathologist. Optimising medical treatment of comorbidities such as asthma is also crucial. Vocal cord dysfunction often leads to a misdiagnosis of asthma and subsequent overtreatment with inhaled corticosteroids; however, the two may coexist.

**Nonasthmatic eosinophilic bronchitis**
Nonasthmatic eosinophilic bronchitis is an increasingly recognised cause of chronic cough, usually with minimal sputum production. However, induced sputum in these patients demonstrates increased eosinophil counts. Typically, the patient has no airflow limitation on spirometry and no bronchial hyper-reactivity on bronchial challenge test. These results suggest active airway inflammation in the absence of airway hyper-responsiveness. Treatment with inhaled corticosteroids should alleviate the cough within four weeks of therapy.

**Chronic lung diseases**
Patients with chronic lung diseases often have persistent cough, with excessive sputum production seen in those with conditions such as chronic bronchitis and bronchiectasis. Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction and is usually progressive, with enhanced chronic airway inflammation to noxious particles. The clinical diagnosis should be suspected in patients with dyspnoea, chronic
cough or sputum production, and exposure to risk factors (e.g. tobacco smoke, pollution, burning of biomass fuels). Assessment and management of patients with COPD should be guided by established guidelines (e.g. Global Initiative for Chronic Obstructive Lung Disease guidelines).\(^\text{35}\)

Bronchiectasis shares many clinical features with COPD. Clinical diagnosis can be established by chronic daily cough with viscid sputum production and a high-resolution CT scan of the chest demonstrating bronchial thickening and luminal dilatation. This could be due to a congenital condition, such as cystic fibrosis, ciliary dyskinesia or immunodeficiency, or acquired through recurrent or significant airway insults, such as childhood infections, foreign body aspiration or connective tissue disease. Treatment aims at controlling infection and improving bronchial hygiene. Referral of the patient to a respiratory physician with support of a multidisciplinary team (including a physiotherapist and pulmonary rehabilitation) is recommended.

**Asthma**

Asthma is a common cause of chronic cough and should be considered once upper airway cough syndrome has been evaluated. Medical history is not reliable to exclude the diagnosis and the bronchoprovocation test, which has a high negative predictive value and a positive predictive value of 60 to 88%,\(^\text{22,36}\) is often needed.\(^\text{17}\) Most patients will respond to treatment including inhaled corticosteroids and β-agonists within one week, but complete resolution may take up to eight weeks or more. If cough persists, a 5- to 10-day trial of oral corticosteroids may be required (see the section on asthma under the acute cough heading).

**Obstructive sleep apnoea**

Obstructive sleep apnoea is characterised by symptoms of snoring, observed apnoeic episodes during sleep (with or without nocturnal awakenings) and daytime hypersomnolence. Overnight polysomnography remains the standard for diagnosis. Management includes weight loss advice, nasal continuous positive airway pressure and mandibular splinting devices, depending on severity.

**Gastro-oesophageal reflux disease**

Up to a third of patients with GORD may experience chronic cough,\(^\text{38}\) suggested by association of cough with meals, worsening on supine/stooping posture or the presence of dyspepsia. Reflux-associated cough may also affect patients without noticeable gastro-oesophageal symptoms. The most useful test for GORD is 24-hour ambulatory oesophageal pH monitoring. However it is not routine to put patients through such a test. Antireflux treatment reduces cough reflex sensitivity in affected patients so a trial of acid suppressants may be warranted without investigation. Proton pump inhibitors, with or without prokinetic agent cover, for at least eight weeks are recommended.\(^\text{29}\) However, if the cough persists, acid suppressants should be discontinued after the recommended trial period.

**‘Unexplained cough’**

Occasionally cough persists despite addressing the acute and chronic causes described above. A trial of empirical treatment with inhaled corticosteroids, proton pump inhibitors and speech pathologist review are recommended by some authors.\(^\text{22}\) Referral of the patient to a respiratory specialist centre may also assist, especially if conditions such as refractory asthma and eosinophilic bronchitis are suspected.

**CONCLUSION**

Cough is one of the most common causes of presentations to primary care physicians, and can be challenging from a diagnostic and therapeutic viewpoint. Chronic cough can be disabling and places a significant cost burden on our health system. Viral upper respiratory tract infections are the most common cause of an acute cough and are usually self-limiting. Smoking is the most common cause of chronic cough; with asthma, GORD and upper airway cough syndrome being the most common causes in nonsmokers.

An effective management plan is important in the evaluation and treatment of cough. Clinicians should take a thorough history and perform a physical examination, as well as targeting investigations, providing adequate treatment trials and canvassing the option of combining therapeutic approaches. It is important to determine early whether a serious underlying cause such as malignancy, pneumonia or congestive cardiac failure is present. In difficult or undiagnosed cases, clinicians should refer the patient to a specialist with an interest in chronic cough management.

**Competing Interests**

Dr Kwan receives honoraria for speaking at GP meetings from GlaxoSmithKline and AstraZeneca. Dr Chin: None.
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ALDARA™ is recommended as first intention by the following guidelines:

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- ECPHPV (European Course on HPV Associated Pathology)
- American Medical Association Consensus Conference
- Sexually Transmitted Diseases Treatment Guidelines 2002 CDC (Centers for Disease Control and Prevention)

ALDARA™ Cream Reducing the recurrence rate

Sustained clearance and wart recurrences during 6-month follow-up (% of subject)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sustained clearance</th>
<th>Recurrence</th>
<th>Lost to follow-up/missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=92)</td>
<td>64</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>B (n=100)</td>
<td>89</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>C (n=75)</td>
<td>65</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

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MANAGING COUGH IN ADULTS
IS THERE A SERIOUS UNDERLYING CAUSE?

SECTION A.

QUESTION 1. Which of the following is the correct definition of acute cough? Choose the best answer.
A. Cough that starts abruptly
B. Cough lasting more than three weeks
C. Cough lasting less than three weeks
D. Cough lasting between three and four weeks

Case study 1. Ali, aged 21 years, has had a cough for two weeks. She was previously well, then had a flu-like illness. All her symptoms settled after a few days except for the cough. Her physical examination is normal. She is a nonsmoker and does not drink alcohol.

QUESTION 2. Which one of the following is the most likely cause of Ali's cough?
A. Pneumonia
B. Viral upper respiratory tract infection
C. Asthma
D. Exacerbation of chronic obstructive pulmonary disease (COPD)

Case study 1 (continued). Next you start to think about investigations.

QUESTION 3. Which one of the following statements regarding investigations is correct in Ali's case?
A. Spirometry should be performed
B. Chest x-ray should be performed
C. CT scan of the chest should be performed
D. No investigations are needed

Case study 1 (continued). Ali is getting little sleep at night because she can't stop coughing and is worried about her studies.

QUESTION 4. Which two of the following treatments could you suggest for Ali?
A. Nasal decongestant
B. Codeine
C. Dextromethorphan
D. Acid suppressing agents

QUESTION 5. Certain medications can cause cough. Patients often forget to mention over-the-counter preparations when listing their medications to doctors. How can you get an accurate medication history? Select as many answers as you think appropriate.
A. Ask patients to bring all their medications in
B. Arrange a Home Medicines Review
C. Get collateral history
D. Other – please write the strategies you use
SECTION B.

QUESTION 6. Which three of the following are the most likely causes of chronic cough in people who are nonsmokers with no recent chest infection and a normal chest x-ray?

A. Upper airway cough syndrome  
B. Asthma  
C. Psychogenic cough  
D. Gastro-oesophageal reflux disease

Case study 2. Pauline, aged 67 years, comes to see you today because she has been coughing most days for the past 10 weeks or so. She is very worried and thinks there must be something seriously wrong with her.

QUESTION 7. List at least three symptoms you would enquire about when taking a history from Pauline.

Case study 2 (continued). You learn that Pauline has smoked 10 cigarettes a day since the age of 45 years. Her cough has no mucus or blood in it. She has not experienced any fevers, night sweats, weight loss or aches and pains.

QUESTION 8. Which two of the following are first-line investigations that should be performed in this case?

A. Measurement of oestrogen levels  
B. Chest x-ray  
C. CT scan of the chest  
D. Spirometry

Case study 2 (continued). Pauline’s investigations are normal. However, she now mentions that she has had indigestion for a while now, but ‘didn’t think anything of it’. You suspect that her cough might be associated with her indigestion and that she may have gastro-oesophageal reflux disease (GORD).

QUESTION 9. State how you would determine that Pauline’s cough is reflux-associated?

Question 10. Occasionally a cause cannot be found for a cough. State how such patients should be managed.
Methods Effectiveness of Insulin Delivery and Glucose Monitoring in Diabetes Mellitus

BACKGROUND

Diabetes mellitus is a group of metabolic diseases resulting from defects in insulin secretion from the pancreatic beta-cells, resistance to insulin action at the tissue level, or both. The resultant hyperglycemia, if untreated, can lead to long-term complications, including microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary heart disease and cerebrovascular disease). In pregnant women with pre-existing diabetes, poor glycemic control is associated with poorer pregnancy outcomes, including fetal anomalies, macrosomia, delivery complications, stillbirth, and neonatal hypoglycemia.

RESEARCH FOCUS

In response to a public request regarding the benefits and harms of current modes of intensive insulin therapy (continuous subcutaneous insulin infusion [CSI] vs. multiple daily injections [MDI]) and modes of blood glucose monitoring (real-time continuous glucose monitoring [rt-CGM] vs. self-monitoring of blood glucose [SMBG]), the Agency for Healthcare Research and Quality (AHRQ) contracted with the Evidence-based Practice Center at Johns Hopkins University to conduct a systematic review of these modalities. Forty-one studies in 44 publications met the inclusion criteria. Outcomes including glycemic control, hypoglycemia, quality of life, and clinical outcomes were assessed in individuals with type 1 diabetes, type 2 diabetes, or pre-existing diabetes in pregnancy. The review did not include pregnant women with gestational diabetes and patients with maturity-onset diabetes of the young in its evaluation. This summary, based on the full report of research evidence, is provided to assist in decisionmaking along with consideration of a patient’s values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.
Take Steps to Help Protect Them From Pneumococcal Disease

Prevenar 13® is the first and only pneumococcal conjugate vaccine for children aged <5 years and adults aged ≥50 years.5,7

Pneumococcal disease occurs more frequently at extremes of age: in children aged <5 years and adults aged ≥50 years.

Specific conditions like asthma in older children or chronic obstructive pulmonary disease (COPD), cardiovascular disease, and diabetes in adults may also increase the likelihood of pneumococcal disease.5,6

Prevenar 13 is indicated for active immunization for:

- **Infants and children:**
  - the prevention of invasive disease, pneumonia, and acute otitis media caused by Streptococcus pneumoniae in infants, children, and adolescents from 6 weeks to 5 years of age.
- **Adults ≥50 years of age:** the prevention of invasive disease caused by S pneumoniae.

Prevenar 13 is the most widely used PCV in the world.6

Help protect your patients by vaccinating them with Prevenar 13

**Indications**

- Prevenar 13 is indicated for active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae in adults ≥50 years of age and the elderly.
- Prevenar 13 is indicated for active immunization for the prevention of invasive disease, pneumonia, and acute otitis media caused by S pneumoniae in infants, children, and adolescents from 6 weeks to 5 years of age.

**IMPORTANT SAFETY INFORMATION**

- The approval of Prevenar 13 was based upon antibody responses in children and adults. Prevenar 13 has not been shown to reduce morbidity or mortality due to invasive or noninvasive pneumococcal disease in adults.
- Hypersensitivity (eg, anaphylaxis) to any component of Prevenar 13 or any diphtheria toxoid–containing vaccine is a contraindication to the use of Prevenar 13.
- As with any vaccine, Prevenar 13 may not prevent disease in all vaccinated individuals.
- The frequency of pneumococcal serotypes and serogroups varies geographically, and could influence the effectiveness of the vaccine in any given country.
- Because otitis media or pneumonia can be caused by organisms other than the serotypes of S pneumoniae represented in the vaccine, protection against all otitis media or pneumonia is expected to be lower than for IPD.
- In clinical studies with concomitant administration of Prevenar 13 and rotavirus vaccine in children, no change in the safety profiles of these vaccines was observed; immunogenicity was not evaluated.

**References:**


Please see Product Information.

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The prevalence of diagnosed diabetes in the United States is currently 7.7 percent and is expected to increase to nearly 10 percent by 2050. Daily insulin therapy is vital in the 5 to 10 percent of patients with type 1 diabetes and may be required in the 90 to 95 percent of patients with type 2 diabetes.

For tight glycemic control, insulin is administered according to the basal-prandial strategy. This can be done either via MDI or CSII. Glycemic control with intensive insulin therapy (either via MDI or CSII) has been shown to reduce the risk of the microvascular and macrovascular complications of diabetes. However, tight glycemic control can be associated with an increased risk of hypoglycemia for glycemic control, while intensive insulin therapy can lead to weight gain.

While long-term glycemic control in individuals with type 1 or type 2 diabetes is assessed by measuring hemoglobin A1c (HbA1c), fasting and 2-hour postprandial blood glucose are measured for short-term adjustments in insulin therapy. Monitoring of blood glucose is performed either through SMBG or rt-CGM.

The comparative effectiveness of CSII and MDI in young and old patients with type 1 diabetes, patients with type 2 diabetes, and pregnant women with pre-existing diabetes have not been systematically assessed. Additionally, the relative benefits of glucose monitoring with SMBG versus rt-CGM remain to be systematically evaluated.

### CLINICAL BOTTOM LINE

#### Insulin Delivery: MDI Versus CSII

**Children and Adolescents With Type 1 Diabetes**
- HbA1c lowering did not differ significantly between CSII and MDI (mean difference from baseline, -0.14%; 95% CI, -0.48 to 0.20; p = 0.41).
- Frequency of daytime hypoglycemia, frequency of nocturnal hypoglycemia, rate of severe hypoglycemia, weight gain, and quality of life did not differ significantly between CSII and MDI.
- CSII was associated with a significant improvement in diabetes treatment satisfaction versus MDI (mean difference, 5.7; 95% CI, 5.0 to 6.4; p < 0.001).

**Adults With Type 1 Diabetes**
- CSII resulted in a significant HbA1c-lowering effect when compared with MDI (mean difference from baseline, -0.30%; 95% CI, -0.58 to -0.02), although results were heavily influenced by one study.
- Frequency of nocturnal hypoglycemia, severe hypoglycemia, other nonsevere hypoglycemia, hyperglycemia, and weight gain did not differ significantly between CSII and MDI.
- CSII resulted in a small decrease in postprandial glucose and an increase in symptomatic hypoglycemia when compared with MDI.
- CSII was associated with a significant improvement in diabetes-specific quality of life compared with MDI (mean difference, 2.99; 95% CI, 0.006 to 5.97; p = 0.05).

**Adults With Type 2 Diabetes**
- HbA1c lowering did not differ significantly between MDI and CSII (mean difference from baseline, -0.16%; 95% CI, -0.42 to 0.09; p = 0.21).
- No significant between-group differences in frequency of mild hypoglycemia (or severe hypoglycemia or in weight gain were observed in this population).

**Pregnant Women With Pre-existing Type 1 Diabetes**
- HbA1c improved in both the CSII and MDI arms in all three trimesters, with no significant differences between the two arms.

#### Glucose Monitoring: rt-CGM Versus SMBG

**Children and Adults With Type 1 Diabetes**
- rt-CGM was associated with a significant HbA1c-lowering effect when compared with SMBG (mean difference from baseline, -0.30%; 95% CI, -0.37 to -0.22%; p < 0.001).
- Time spent in the hypoglycemic range (mean difference, 2.11 minutes/day; 95% CI, -5.66 to 1.44 minutes/day) was similar in the rt-CGM and SMBG groups.
- A significant reduction in time spent in the hyperglycemic range occurred with rt-CGM when compared with SMBG (-68.56 minutes/day; 95% CI, -101.17 to -35.96).
- The evidence was inconsistent for the effect of rt-CGM versus SMBG on the ratio of basal to bolus* insulin in a daily insulin dose.
- The rt-CGM and SMBG groups exhibited similar rates of severe hypoglycemia, general quality of life, and diabetes-specific quality of life.

* rt-CGM was associated with a significant HbA1c-lowering effect when compared with SMBG (mean difference from baseline, -0.30%; 95% CI, -0.37 to -0.22%; p < 0.001).
approach to intensive insulin therapy can therefore be individualized to the preferences of appropriate patients that will maximize their quality of life. Studies suggested that rt-CGM was superior to SMBG in lowering HbA1c in nonpregnant individuals with type 1 diabetes, particularly when compliance was high, without affecting the risk of severe hypoglycemia. rt-CGM/CSII in the form of sensor-augmented pumps was superior to MDI/SMBG in lowering HbA1c in the research studies analyzed in this review; however, other combinations of these insulin delivery and glucose monitoring modalities were not evaluated.

**GAPS IN KNOWLEDGE**

Several shortcomings exist in the studies examining the effects of insulin delivery and glucose monitoring devices reviewed for this report.

- Most randomized controlled trials identified in the literature were small, with the largest study including 322 participants.
- Most studies, particularly those comparing CSII with MDI, were fair to poor in quality and did not report most outcomes of interest.
- Most studies did not report the racial and ethnic composition of the study populations; for those that did, the study populations were mainly white and had limited numbers of participants from other ethnic groups in which diabetes is more prevalent.
- Few studies focused on or included children 12 years of age or younger or adults 65 years of age or older.
- The studies varied widely in definitions of nonsevere hypoglycemia, hyperglycemia, and weight gain, thus not permitting definitive conclusions about the effects of insulin delivery and glucose monitoring strategies on these intermediate outcomes.
- None of the studies included data on long-term microvascular and macrovascular complications associated with diabetes.
- Studies failed to evaluate insulin delivery and glucose monitoring devices in pregnant women with pre-existing type 2 diabetes, and

### CLINICAL BOTTOM LINE (continued)

**rt-CGM Plus CSII (Sensor-Augmented Pump) Versus MDI/SMBG**

**Children and Adults With Type 1 Diabetes**

- Using a sensor-augmented pump was associated with a significant HbA1c-lowering effect when compared with SMBG (mean difference from baseline, -0.68%; 95% CI, -0.81 to -0.54%; *p* < 0.001).
- Time spent with nonsevere hypoglycemia and incidence of severe hypoglycemia were similar between the sensor-augmented pump and the MDI/SMBG groups.
- Overall diabetes treatment satisfaction was greater among participants in the sensor-augmented pump arm when compared with the MDI/SMBG arm, while no significant difference was observed in weight gain between the two arms.
- Evidence from two randomized controlled trials suggests that time spent with hyperglycemia is significantly lower in the sensor-augmented pump group versus the MDI/SMBG group (*p* < 0.001).

**Strength of Evidence Scale**

- **High:** High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate:** Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low:** Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient:** Evidence is either unavailable or does not permit a conclusion.

### CONCLUSION

Both CSII and MDI had similar effects on glycemic control and rates of severe hypoglycemia in children and adolescents with type 1 diabetes and adults with type 2 diabetes. In contrast, some studies suggested that CSII was superior to MDI for glycemic control in adults with type 1 diabetes with no difference in hypoglycemia and weight gain. Limited evidence suggested that measures of quality of life or treatment satisfaction improved in patients with type 1 diabetes. The
the studies in pregnant women with pre-existing type 1 diabetes did not examine the effect of rt-CGM on maternal and fetal outcomes.

- Most of the studies did not report the extent of treatment adherence. High baseline HbA1c values in both the CSII and MDI intervention groups may be related to poor adherence to previous treatments.
- The studies were not uniform in assessing and reporting quality-of-life outcomes, thus precluding quantification of the effects of insulin delivery methods and glucose monitoring devices on quality of life.
- Several studies excluded individuals with comorbidities such as impaired liver and renal function, microvascular complications, cardiovascular disease, mental disorders, recent severe hypoglycemia, or other chronic medical conditions, thereby limiting the applicability of the results to the entire population.

These shortcomings highlight the need for future large, well-designed studies with participants of all ages and from diverse ethnic groups, standard outcome measures including measures of vascular complications and quality of life, and long followup duration and for studies in pregnant women with pre-existing type 1 or type 2 diabetes.

**WHAT TO DISCUSS WITH YOUR PATIENTS**

- The role of other lifestyle changes in managing the patient’s diabetes
- The importance of glycemic control in managing the patient’s diabetes
- The role of routine blood glucose monitoring in maintaining appropriate glycemic control
- The available strategies for insulin delivery and blood glucose monitoring
- The available evidence for the effectiveness of MDI versus CSII for insulin delivery
- The available evidence for the effectiveness of SMBG versus rt-CGM for glucose monitoring
- The available evidence for the effectiveness of rt-CGM plus CSII (sensor-augmented pump) versus MDI/SMBG
- The potential risks associated with intensive insulin therapy such as hypoglycemic events and weight gain, their impact on quality of life, and strategies for their management
- The potential out-of-pocket costs that the patient might incur with certain insulin delivery and glucose monitoring modalities based on his/her insurance coverage

**SOURCE**

The information in this summary is based on *Methods for Insulin Delivery and Glucose Monitoring: A Comparative Effectiveness Review*, Comparative Effectiveness Review No. 57, prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I for the Agency for Healthcare Research and Quality, June 2012. Available at www.effectivehealthcare.ahrq.gov/glucose.cfm. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.
NEW YORK (Reuters Health) - Short bursts of intense exercise before meals may help control blood sugar spikes better than one longer, less intense session, suggests a new small study.

Researchers say these “exercise snacks” may be an effective way to improve blood sugar control among people with insulin resistance, a precursor to diabetes.

“Exercise spread across the day reduces sedentary time, and spread before meals reduces blood glucose spikes after meals,” said lead author Monique Francois.

“Exercise on top of an active lifestyle needs to be more intense than we normally do when walking or moving around,” Francois, from the University of Otago in Dunedin, New Zealand, added in an email to Reuters Health.

She explained that exercise, along with insulin, stimulates muscles to take up glucose from the blood.

“Intense exercise (and prolonged exercise)... moves glucose into the muscle quickly and for several hours after,” she said.

“Moving glucose into the muscle so it can be used as fuel or stored lowers blood glucose, as the body only wants a certain amount of glucose in the blood.”

Francois and her colleagues studied two women and seven men diagnosed with insulin resistance. Two of the participants had type 2 diabetes, but none were taking medication for diabetes or blood sugar control.

The participants completed three separate one-day exercise programs in a random order.

The exercise snacks program involved short bouts of intense exercise on a treadmill before breakfast, lunch and dinner. The composite exercise snacks regimen was similar, but included some resistance exercises alternating with walking. The traditional continuous exercise program consisted of 30 minutes of moderate-intensity walking before dinner only.

Meal timing and composition were the same during the three days.

The researchers found that the exercise snacks and composite exercise snacks routines controlled blood sugar more effectively than the continuous exercise routine.

Specifically, there was a 17 percent reduction in glucose levels over the three hours following breakfast and a 13 percent reduction in glucose levels after dinner on the exercise snack days compared to the continuous exercise days.

Across the day this represented a 12 percent reduction in average post-meal blood glucose levels, the authors report in the journal Diabetologia.

This was a small study and more long-term studies need to be done to confirm the results. Francois said she’d also like to learn more about the best time for exercising and how to encourage people to exercise more.
She said high-intensity exercise can be performed in about half the time with similar or greater benefits than low- to moderate-intensity exercise.

“In this study interval exercise using walking uphill or resistance band exercises both improved glucose control similarly - the combination of resistance exercise to exercise the upper body and uphill walking targeting the lower body was chosen to maximize the muscle mass used,” she said.

Francois added that cycling, walking and team sports have all been proven to be effective in helping to control blood sugar levels.

Sheri Colberg-Ochs told Reuters Health the study’s findings are “interesting… not that surprising.”

Colberg-Ochs studies diabetes and exercise at Old Dominion University in Norfolk, Virginia. She wasn’t involved with the new research.

“My main issue with high-intensity intervals like that is that many people with diabetes (not just pre-diabetes, or insulin resistance) really aren’t in any physical shape to undertake that type of exercise, and many of them have undiagnosed (or diagnosed) cardiovascular problems that may make such exercise unsafe for them to undertake as well,” she said.

It’s a risky activity for those patients that doctors would most want to help, Colberg-Ochs said.

“I would suggest instead that the walking be undertaken after eating to have a greater effect at suppressing post-meal rises in blood glucose levels, in case some individuals cannot undertake the ‘exercise snacks,’” she said.

By Shereen Jegtvig

EXERCISE TIED TO DECREASED DIABETES RISK AMONG HIGH-RISK WOMEN

NEW YORK (Reuters Health) - Women who become diabetic during pregnancy may be able to avoid later developing type 2 diabetes with exercise, according to a new U.S. study.

Among women who had so-called gestational diabetes, those who upped their exercise by a little more than 20 minutes a day after giving birth had half the longer-term diabetes risk of women who didn’t change their activity levels.

“This is kind of a hopeful message because they may think they are at a high risk of type 2 diabetes, but this shows they shouldn’t give up,” Dr. Cuilin Zhang said. “Exercise more. It can help.”

Zhang, from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, in Rockville, Maryland, is the study’s lead author.

Women - especially those who are older, heavier and not white - are at risk of developing gestational diabetes, because of changes in the body during pregnancy. Gestational diabetes affects between 2 percent and 10 percent of U.S. pregnancies.
While women with gestational diabetes may experience symptoms typical of type 2 diabetes including increased thirst and urge to urinate, most women find out from their doctors.

If blood sugar isn’t controlled during pregnancy, gestational diabetes puts babies at risk of being born earlier and heavier than normal. It also puts women at increased risk of high blood pressure and preeclampsia, another serious pregnancy complication.

Although gestational diabetes may disappear after childbirth, a woman who has had it is at increased risk of developing type 2 diabetes, especially within the next five years.

“Pregnancy is like a stress test,” Zhang said. “Pregnancy can unveil the high susceptibility of type 2 diabetes later in their lives.”

For the new study, the researchers used 16 years’ worth of data on 4,554 adult women who had a history of gestational diabetes. By the end of the study period, 635 had developed type 2 diabetes.

Based on behaviors like exercise and time spent watching television, the researchers calculated the women’s risk of developing type 2 diabetes.

Among the one-fifth of women who exercised the least, about 19 percent developed diabetes later on, compared to about 9 percent among the one-fifth who exercised the most.

The researchers found that a woman’s risk of developing type 2 diabetes fell by about 9 percent for every additional 100 minutes of moderate-intensity exercise added per week.

Overall, women who increased their exercise by 150 minutes a week had just 53 percent of the diabetes risk of women who didn’t change their activity levels after pregnancy.

Watching television, in contrast, was tied to an increased risk of developing type 2 diabetes. For instance, women who watched 11 to 20 hours of TV a week had 1.4 times the diabetes risk of women who watched 0 to 5 hours a week.

Those results don’t mean that watching television is the problem, the researchers write in JAMA Internal Medicine. Instead, it’s more likely that people who watch a lot of television are generally less healthy than those who don’t.

They caution that the study’s results may not apply to all women because their data primarily come from white women living in the U.S.

Monique Hedderson told Reuters Health that the healthcare system needs to do a better job of understanding what works at preventing type 2 diabetes among high-risk women.

“It’s a challenging time for women during the post partum period when they have a baby,” she said.

Hedderson co-authored a commentary accompanying the new study. She is a research scientist at the Kaiser Permanente Division of Research in Oakland, California.
“It’s important for young women to be physically active before, during and after pregnancy,” she said. “That is the bottom line.”

Zhang said the ultimate goal of their research is to identify how medicine, lifestyle and genetics come together to influence risk among women with a history of gestational diabetes.

By Andrew M. Seaman

PANEL’S REPORT LIKELY TO TIE FARM ANTIBIOTICS TO HUMAN RESISTANCE

CHICAGO (Reuters) - A White House advisory committee is expected to acknowledge the link between antimicrobial resistance in humans and livestock being fed antibiotics when it issues its report in the next few weeks, according to the transcript of a committee meeting held earlier this month.

But how much of the public health problem can be attributed to such farming practices remains unclear, according to the transcript of a July 11 meeting of the President’s Council of Advisors on Science and Technology (PCAST).

Committee members have declined to discuss the report before its release, which is expected to happen in the next few weeks.

In the transcript, council co-Chairman Eric Lander said there was “clear documentation” that antibiotic-resistant microbes can transfer from farm animals to humans.

“That judicious use (of antibiotics) in agriculture right now is absolutely essential,” Lander said in the transcript. “There may come a point where one will say it’s justified to say no use.”

Governments and public health officials worldwide have begun ramping up efforts to fight so-called “super bugs” - microbes that have mutated to be resistant to medically important antibiotics such as cephalosporins, which are used to treat hospital-acquired infections like blood infections and meningitis.

The committee’s report on antibiotic resistance, according to the transcript, is likely to recommend several actions to stay ahead of what Lander described as a “cat-and-mouse game played at this microscopic level between our agents, our therapeutics, and these microbes.”

The actions are expected to include offering government incentives to encourage the development of new antibiotics; setting up a federal inter-agency task force on antibiotic resistance; finding alternatives to human-relevant antibiotics for livestock producers to use to promote animal growth and prevent disease, and increasing the U.S. Food and Drug Administration’s powers to expedite the approval of antibiotics for limited or specialized uses.

In the United States, consumer advocacy groups and some lawmakers have been urging the White House and federal regulators to take a more aggressive stance on how the U.S. livestock industry uses antibiotics and other medications.
U.S. Representative Louise M. Slaughter, a New York Democrat who is the only microbiologist in Congress, sent a letter last week to the president asking for an executive order requiring that all federally purchased meat be raised without antibiotics and calling for the establishment of PCAST’s recommended inter-agency task force, among measures to address the problem.

By P.J. Huffstutter

ROBOT BLADDER SURGERY FAILS TO DELIVER FEWER COMPLICATIONS

NEW YORK (Reuters Health) - Using robotic techniques to remove a cancerous bladder doesn’t reduce the risk of complications compared with conventional “open” surgery, according to a new comparison of 118 patients conducted by surgeons at the Memorial Sloan Kettering Cancer Center in New York. The study, detailed in the New England Journal of Medicine, marks the first ongoing comparison of the risks and benefits of the two techniques. Past studies concluded that the robotic technique meant less time in the hospital and fewer complications but they were done by looking back at the records of already-treated patients.

“There’s been a lot of hype surrounding robots and it’s been hard to gain perspective,” said Dr. Vincent Laudone, one of the coauthors.

Dr. Jennifer Yates, director of minimally invasive urology at the University of Massachusetts Medical School, who was not involved in the test, told Reuters Health that the findings will give surgeons pause because they’re going to be surprised by the results.

Robots have shown to be so valuable for prostate removal, many surgeons were convinced that a similar benefit would appear when they were used for bladder removal, she said. “They’re going to say, ‘Hey, I’m kinda surprised by this!’ They’re also going to be encouraged that the complication rate was comparable.”

“Bottom line: It looks like it was pretty much a wash,” Laudone told Reuters Health. For patients, it means “if you’re going to a surgeon who is experienced in traditional surgery and recommends traditional surgery, that’s a reasonable recommendation.”

He estimated that perhaps 25 percent of bladder cancer removals, known as radical cystectomies, are currently done with robots. The study also found that patients who underwent conventional surgery spent about 28 percent less time in the operating room. They experienced more blood loss - about 5 ounces more - but “with that amount, we wouldn’t expect to see any significant side effect,” Laudone said.

“These results highlight the need for randomized trials to inform the benefits and risks of new surgical technologies before widespread implementation,” he and his colleagues concluded.

About 67,000 bladder tumors are discovered in the U.S. each year and one quarter of them require bladder removal.
The new study involved patients who needed both the bladder and nearby lymph nodes extracted. The men also lost their prostate and the women lost their ovaries, fallopian tubes, uterus and related organs. Even when a $2 million robot was used, conventional surgery was employed to redirect urine to the intestine.

With robot-assisted surgery, 22 percent of the 60 patients had at least one serious complication within the first 90 days. A complication was regarded as serious if it required further surgery, intubation or major rehabilitation. The rate was essentially the same - 21 percent - with traditional surgery.

When the researchers included lesser complications, such as those requiring intravenous medicine or blood transfusion, the risk was 62 percent with robot-assisted surgery versus 66 percent with open surgery.

The average length of hospital stay was eight days for both groups.

But the patients in the robot group spent two hours longer in the operating room. The average time was 5 hours 29 minutes with conventional surgery and 7 hours 36 minutes with robotic assistance.

Both Laudone and Yates said that time difference is expected to shrink as doctors become more adept at working with robots.

“It’s an evolving technology and we’re evolving in our learning to use the robot,” Laudone said. “We’re getting better as robotic surgeons, so operating time is diminishing. With prostate surgery, the same thing was true. Now, in some cases, doing it with the robot is faster. So the time difference is something I think will disappear with more experience.”

Yates cautioned that “this was a small study and I think it needs to be fleshed out with larger numbers. And you have to remember that Sloan Kettering is one of the more prominent high-volume institutions in the country. Whether this is generalizable to other institutions remains to be seen.”

By Gene Emery
MANAGING SEVERE COPD: MUCH CAN BE DONE.
CME ANSWERS FOR SEPTEMBER 2014

SECTION A.

Case study. Clem is 76 years old and has severe COPD. You have been his GP for the past 10 years. His 78-year-old wife is his main carer and he has a home care package. You have recently started visiting Clem at home, as he has become housebound. His current medications are salbutamol, tiotropium, paracetamol, aspirin, atorvastatin and, as required, sublingual nitrate.

QUESTION 1. Which two of the following statements are correct of COPD?

b,d. Correct. A careful history and clinical examination may suggest a diagnosis of COPD but they do not reliably predict airflow obstruction and spirometry is essential to confirm the diagnosis. Patients with very severe COPD may have symptoms as debilitating as those with advanced cancer.

a. Incorrect. Access Economics estimated in 2008 that about 150,000 (not 50,000) people had severe COPD and more than one million people had moderate COPD.

c. Incorrect. The degree of airflow obstruction alone may be poorly predictive of symptoms. Guidelines recommend assessing symptom burden (especially the degree of dyspnoea), degree of activity limitation and frequency of exacerbation, along with FEV1, when determining treatment needs.

Case study (continued). You review Clem’s current symptoms.

QUESTION 2. Which of the following are symptoms of very severe COPD? Choose the best answer.

d. Correct. A cardinal feature of very severe COPD is profound dyspnoea. Cough, fatigue, poor social functioning, high rates of depression and anxiety and poor quality of life are also prominent symptoms. Patients with very severe COPD may have symptoms as debilitating as those with advanced cancer. Carers of people with very severe COPD also have significant morbidity.

d. Incorrect. An adverse drug reaction is unlikely to be contributing to Clem’s poor exercise tolerance.

QUESTION 3. Which three of the following may be contributing to Clem’s poor exercise tolerance?

b,c. Correct. Continued limitation of daily activities and worsening symptoms (despite reduced activities) induces deconditioning. This results in an ongoing dynamic of symptoms (such as dyspnoea and depression) affecting activities, and vice versa, often referred to as the ‘dyspnoea spiral’ or downward cycle of deconditioning with worsening symptoms and further restriction of activity.

Case study (continued). Clem is very short of breath even at rest, and tells you he barely moves from his chair throughout the day.

d. Incorrect. Pulmonary rehabilitation improves dyspnoea, exercise capacity and health related quality of life as well as improving symptoms of anxiety and depression and reducing health care utilisation, and may be beneficial for patients all stages of COPD severity. Review of inhaler technique should be repeated at each visit since inadequate device use is very common in patients with COPD.

a. Incorrect. The inflammatory response in COPD is relatively corticosteroid-insensitive (not sensitive).

b. Incorrect. There is some evidence that a combination of a long-acting anticholinergic and a long-acting beta agonist has benefits over either monotherapy.

QUESTION 4. Which two of the following statements are correct of therapy in patients with COPD?

c,d. Correct. Pulmonary rehabilitation improves dyspnoea, exercise capacity and health related quality of life as well as improving symptoms of anxiety and depression and reducing health care utilisation, and may be beneficial for patients all stages of COPD severity. Review of inhaler technique should be repeated at each visit since inadequate device use is very common in patients with COPD.

a. Incorrect. The inflammatory response in COPD is relatively corticosteroid-insensitive (not sensitive).

b. Incorrect. There is some evidence that a combination of a long-acting anticholinergic and a long-acting beta agonist has benefits over either monotherapy.

QUESTION 5. Discussing advance care planning with patients with severe illness, such as severe COPD can be difficult. What can your practice do to support this? Select as many answers as you think appropriate.

Correct. All of the above answers are correct. There is no one correct answer. The purpose of this question is for you to consider and provide practical ideas and methods by which your practice systems can be improved or streamlined.
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* p<0.05  ** p<0.01  † p<0.0001

References
QUESTION 6. Which two vaccinations are recommended for all patients with COPD?

a, c. Correct. Annual influenza vaccinations and up-to-date pneumococcal vaccination are recommended in guidelines for all patients with COPD.

b. Incorrect. Although patients should keep their tetanus vaccination up to date, this is not specifically recommended for patients with COPD.

d. Incorrect. Hepatitis B vaccine is not recommended routinely to patients with COPD.

Case study (continued). Clem eats very little and has lost a considerable amount of weight since your last visit. He seems anxious and lonely, and his wife is worried about him.

QUESTION 7. Which one of the following is the most frequent and important of all COPD comorbidities?

a. Correct. Cardiovascular disease is the most frequent and most important of all COPD comorbidities and may contribute significantly to disease burden.

b. Incorrect. Lung cancer is not the most frequent comorbidity in patients with COPD.

c. Incorrect. Although osteoporosis is a major comorbidity in patients with COPD, it is not the most common comorbidity.

d. Incorrect. Although patients with COPD have an increased prevalence of depression, it is not the most common comorbidity.

QUESTION 8. List at least two indicators in patients with COPD that flag the need for arterial blood gas measurement.

Indicators suggesting a need for measurement of arterial blood gases in patients with COPD include: right heart failure presenting as ankle oedema or raised jugular venous pressure; the presence of cyanosis or polycythaemia; known very severe COPD with FEV1 less than 30%; and pulse oximetry reading less than 92%.

QUESTION 9. Which three of the following statements are correct regarding oxygen therapy in patients with severe COPD?

b, c, d. Correct. Current consensus suggests that nocturnal oxygen therapy may be indicated in patients whose nocturnal arterial oxygen saturation repeatedly falls below 88% or who have evidence of hypoxia-related sequelae. Australian guidelines recommend oxygen therapy should only be provided to those who have ceased smoking. It is important to explain to patients that the indication for long-term oxygen use is the presence of hypoxaemia but that there may be no improvement in dyspnoea through its use.

a. Incorrect. Oxygen therapy for at least 15 hours per day has been shown to prolong life when a patient’s PaO2 is 55 mmHg or below (not 75 mmHg).

d. Incorrect. Although patients with COPD have an increased prevalence of depression, it is not the most common comorbidity.

c. Incorrect. Although osteoporosis is a major comorbidity in patients with COPD, it is not the most common comorbidity. Australian guidelines recommend oxygen therapy should only be provided to those who have ceased smoking. It is important to explain to patients that the indication for long-term oxygen use is the presence of hypoxaemia but that there may be no improvement in dyspnoea through its use.
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Clinically proven all-round brain development:
- Improved Mental Development Index (MDI) by +7 points at 18 months[^2]

Clinically proven all-round brain development:

Improved Mental Development Index (MDI) by +7 points at 18 months[^2]

**Mean MDI**

<table>
<thead>
<tr>
<th>Formula Type</th>
<th>MDI Score</th>
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<tr>
<td>Standard</td>
<td>100</td>
</tr>
<tr>
<td>DHA + ARA</td>
<td>107.6</td>
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