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Time for a Relevant Randomized Controlled Trial of Vena Cava Filters

To the Editor:

Members of the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) Study Group originally published their results in 1998¹ and reported their 8-year follow-up in 2005,² both of which have been widely cited. The PREPIC study demonstrated that although vena cava filters (VCFs) facilitated a decrease in pulmonary embolism (PE), patients with filters had a concurrent increase in deep venous thrombosis (DVT) without a survival benefit. A journal citation report through July 2012 on Web of Science indicates that the PREPIC study, as the only randomized controlled trial of VCFs, has been cited 601 times in the literature and thus has likely impacted the use of VCFs for venous thromboembo-

lism (VTE) in the United States. However, it is critically important for physicians to understand the shortcomings of the study.

The PREPIC study was composed of patients who would not have received a VCF in the United States. The investigators inserted VCFs in patients with active VTE who were receiving therapeutic anticoagulation. At the start of the PREPIC study, the third edition of the American College of Chest Physicians consensus statement, Antithrombotic Therapy for Therapy of Venous Thromboembolic Disease, recommended VCFs for patients with DVT or PE with contraindications to therapeutic anticoagulation or recurrent emboli despite anticoagulation, not in addition to anticoagulation.³ The ninth edition of the consensus statement clearly recommends against VCF use in patients who can instead receive therapeutic anticoagulation; however, VCF use may be appropriate for patients with recurrent PE

while on therapeutic anticoagulation.⁴ As such, recurrent PE and, especially, fatal PE in patients receiving therapeutic anticoagulation are uncommon. Therefore, a decrease in mortality would not be expected.

Recurrent DVTs are expected to be more prevalent in patients with chronic thrombophilic conditions, such as advanced malignancies, compared with patients with reversible (or provoked) conditions, such as traumatic injuries. The PREPIC study did not stratify patients in this manner, and its data diverge from that of other investigations, albeit not randomized controlled trials. For example, although VCF use in patients with cancer is not clearly defined, Schunn et al⁵ documented that 134 (2.2%) of 5970 patients with cancer, contraindications to anticoagulation therapy, and subsequent VCFs developed VTE. Researchers at MD Anderson Cancer Center reported a 1.3% PE rate and a 4.5% caval thrombus rate among 308 patients with a VCF.⁶ A Memorial Sloan-Kettering Cancer Center report⁷ showed a 2% rate of recurrent PE and a 6% rate of recurrent DVT in cancer patients with a VCF. Patients with all stages of malignancy were included in these analyses. Notably, recurrent DVT and PE rates in these patient groups are much lower than reported in PREPIC.

It is well known that subtherapeutic warfarin puts patients at an increased risk for recurrent VTE. The PREPIC investigators reported that warfarin was prescribed for 91% of their patients at discharge with 94% receiving warfarin at 3 months.¹ At 2 years, 38% of both groups were still receiving warfarin. Despite receiving anticoagulation therapy, 20.8% of patients with VCFs and 11.6% without VCFs had

developed recurrent DVT at 2 years.¹ At 8 years, 35.7% of patients with VCFs and 27.5% without VCFs developed recurrent DVT.² This finding contrasts with findings in a study by Billet et al,⁸ in which no statistically significant differences in DVT rates were found among patients with and patients without VCFs. Furthermore, the documented percentage of time that patients were in the therapeutic range for the international normalized ratio was just over 50%.⁸ There was no evaluation of time in therapeutic range among patients enrolled in the PREPIC study. Could the differences in the DVT rates among PREPIC study patients be potentially related to subtherapeutic warfarin therapy?

The most important shortfall of the PREPIC study is extrapolating the use of permanent devices to newer retrievable or “optional” VCFs. Of the filters used in the PREPIC study, the Cardial filter (C.R. Bard Inc, Saint-Etienne, France) has not been approved for use in the United States. The VenaTech LGM filter (B. Braun Melsungen AG, Boulogne, France) was used in 56% of PREPIC patients but has shown a long-term progressive decrease in caval patency to 66.8% at 9 years; this finding was unaffected by age, sex, level of DVT, risk factors, or anticoagulant use.⁹ Post-VCF DVT was not analyzed by filter. Was the increase in DVT the result of using “inferior” VCFs? Would the retrieval of an optional device after the high-risk period for PE passes reduce long-term DVT rates?

For patients with contraindications to therapeutic anticoagulation, use of VCFs in the setting of an acute VTE would be appropriate. Importantly, all VCFs are prophylactic because the purpose of insertion is to prevent further PEs and

not to manage an already present PE or DVT. Patient accrual for the PREPIC study occurred before the advent of the study and widespread use of retrievable VCFs. However, the rate of use of optional VCFs has dramatically increased. As technology has improved outcomes with the use of optional VCFs, there are potential advantages of these devices compared with permanent filters regarding inferior vena caval patency and long-term complications.

The cost of managing a pulmonary embolism is significant,¹⁰ as is the cost of inserting (and removing) a VCF. Now is the time for a multicenter prospective examination of current optional VCFs. The challenge is to characterize and identify the patient group that will benefit from a VCF, as well as to identify patients who will ultimately benefit from removal of the devices when the PE risk has resolved. Because such a study would be managed in a controlled fashion and clear guidelines would be created for placement and removal, findings could result in a “best practices model” for all.

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Update on Advisory Committee on Immunization's Practices (ACIP) Vaccine Recommendations, October 2012

To the Editor:

At its October 2012 meeting, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) approved and provided the following recommendations and updates:

- Tdap (combined tetanus, diphtheria and pertussis) immunization during every pregnancy
- Hib-MenCY-TT (GlaxoSmithKline) meningococcal vaccination down to age 2 months for high risk infants only
- measles–mumps–rubella (MMR) vaccine updates for select immunocompromised patients
- combined pediatric immunization schedule for 2013
- quadrivalent influenza vaccine expected to be available as a live attenuated influenza vaccine and inactivated vaccines for the 2013-2014 influenza season
- Centers for Medicare & Medicaid Services (CMS) incentive reimbursement to primary care providers for administration of immunizations

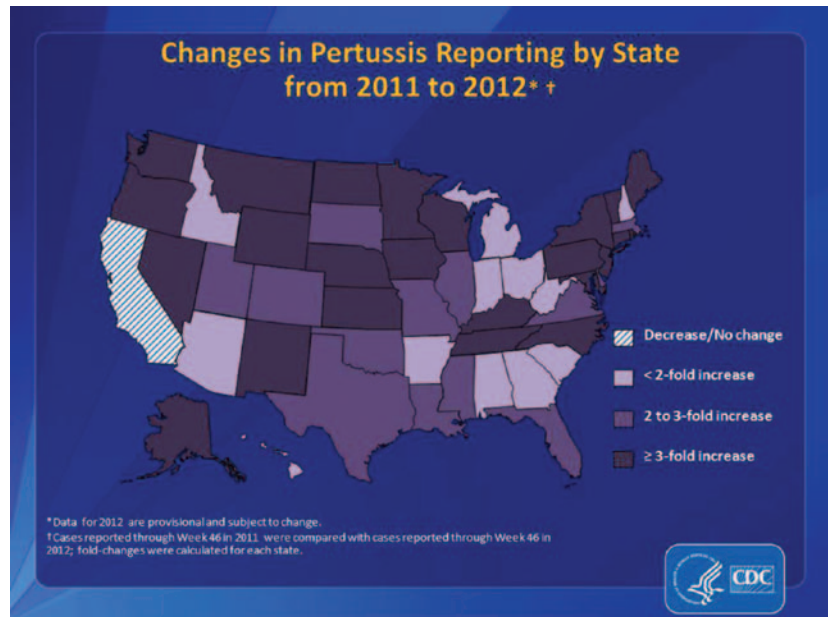


Figure. Pertussis incidence by state, 2011-2012.¹

Tdap Immunization During Pregnancy

Recent outbreaks of pertussis in Washington State and other areas of the United States (*Figure*) resulted in the ACIP voting to take additional steps to protect mothers, fetuses, and infants from pertussis by recommending Tdap immunization for all pregnant women. As stated in a media release² from the CDC,

Health-care personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum.

Hib-MenCY-TT Meningococcal Vaccine for High-Risk Infants

The ACIP recommended that infants who are at increased risk for meningococcal disease should receive 4 doses of the Hib-MenCY-TT vaccine at ages 2, 4, and 6 months and between ages 12 and 15 months.³

Children at risk include those with recognized persistent complement pathway deficiencies and those with anatomic or functional asplenia, including sickle cell disease. The vaccine also can be used in infants aged 2 to 18 months who live in communities with outbreaks of serogroup C and Y meningococcal disease.³ However, the newly approved vaccine is not recommended as a routine meningococcal vaccination for infants because the amount of preventable meningococcal disease cases in children younger than 5 years is low and because

for those younger than 1 year, most cases are caused by serogroup B, which the vaccine does not protect against.³

MMR Vaccine

Intramuscular immune globulin prophylaxis for measles after exposure is recommended at a dose of 0.5 mL/kg of body weight, with a maximum dose of 15 mL.⁴ The dosage of intravenous immune globulin is 400 mg/kg.⁴ Other recommended updates include the following⁴:

- Intramuscular immune globulin should be given to infants younger than 12 months who have been exposed to measles. For infants aged 6 to 11 months, the MMR vaccine can be given in place of intramuscular immune globulin if administered within 72 hours of exposure.
- Intravenous immune globulin should be given to pregnant women who do not have evidence of measles immunity and who have been exposed to measles.
- Intravenous immune globulin should be given to immunocompromised persons without evidence of measles immunity and who have been exposed to measles.
- Asymptomatic individuals with HIV who do not have evidence of severe immunosuppression (CD4 cell count <15%) should receive the vaccine. Consideration should be given to administering a second dose 28 days after the first dose.
- Individuals with perinatal HIV infection who were vaccinated prior to establishment of effective

antiretroviral therapy should be revaccinated.

- The distinction between asymptomatic and symptomatic HIV infection should be removed.
- The timing of the 2 doses should be changed to ages 12 through 15 months and ages 4 through 6 years.

Once these revised recommendations are accepted by the director of the CDC and the secretary of the US Department of Health and Human Services, they will be published in the CDC's *Morbidity and Mortality Weekly Report (MMWR)*.

Combined Pediatric Immunization Schedule

The new pediatric schedule will combine the 0- to 6-month and 7- to 18-month schedules into 1 schedule.⁵ The footnotes will be on separate pages with a larger font to make them more readable. The catch-up schedule will remain as a separate schedule. The 2013 pediatric schedule is scheduled to be published in the *MMWR* in February 2013 pending approval by the American Academy of Pediatrics and the American Academy of Family Physicians.⁵

Influenza Vaccines

As reported in an August 2012 article in *MMWR*,⁶

In February 2012, [the] FDA [Food and Drug Administration] approved a new seasonal quadrivalent LAIV [live-attenuated influenza vaccine], FluMist Quadrivalent (Medimmune). This vaccine currently is not anticipated to be available until the 2013–14 influenza season, at which time it is expected to replace the currently available

seasonal trivalent FluMist formulation. Inactivated quadrivalent influenza vaccines currently are in development. These vaccines will be addressed in the ACIP influenza statement as they are approved and become available commercially.

The CDC believes that the quadrivalent vaccine could result in a “modest reduction in influenza-associated outcomes.”⁶

Incentive Reimbursement to Primary Care Providers

The CMS will be implementing an increase in Medicaid payment rates for certain primary care and immunization services to at least those of Medicare level.⁷ The rule extends the payment increase to physicians with a primary specialty designation of family medicine, general internal medicine, or pediatric medicine, and it specifies that the increase will also apply to many pediatric subspecialists. The payment increase takes effect in 2013 and extends through the end of 2014.⁸

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Financial Disclosures:

Dr Grogg is a primary investigator for vaccine research and has received grants from GlaxoSmithKline plc; Merck & Co, Inc; MedImmune LLC; Novartis Pharmaceuticals; Pfizer Inc; and sanofi-aventis US LLC. He serves on the speakers' bureaus for MedImmune LLC; Merck & Co, Inc; Novartis Pharmaceuticals; and sanofi-aventis US LLC. He is also a consultant for Merck & Co, Inc (for the human papillomavirus), and Novartis Pharmaceuticals (for meningitis).

Corrections

The *JAOA* regrets an error that appeared in the following article:

Przekop P, Haviland MG, Zhao Y, Oda K, Morton KR, Fraser GE. Self-reported physical health, mental health, and comorbid diseases among women with irritable bowel syndrome, fibromyalgia, or both compared with healthy control respondents. *J Am Osteopath Assoc*. 2012;112(11):726-735.

In *Table 2*, the third, fifth, seventh, and ninth column heads incorrectly appeared as Mean (SD). These headings should have appeared as No. (%).

In addition, the *JAOA* and the authors regret an error that appeared in the following article:

Ghayad Z, Hou C. Erythema migrans in early disseminated Lyme disease [Clinical Images]. *J Am Osteopath Assoc*. 2012;112(11):748.

In the final sentence of the article, the term *late-stage Lyme disease* was incorrect. The sentence should have read: Physicians should be aware of potential complications with *early stage Lyme disease*, including uveitis and other tick-borne diseases.

These corrections will be made to both the full text and PDF versions of the articles online.

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