CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Technologic Advances in Endotracheal Tubes for Prevention of Ventilator-Associated Pneumonia

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Ventilator-associated pneumonia (VAP) is associated with high morbidity, mortality, and costs. Interventions to prevent VAP are a high priority in the care of critically ill patients requiring mechanical ventilation (MV). Multiple interventions are recommended by evidence-based practice guidelines to prevent VAP, but there is a growing interest in those related to the endotracheal tube (ETT) as the main target linked to VAP. Microaspiration and biofilm formation are the two most important mechanisms implicated in the colonization of the tracheal bronchial tree and the development of VAP. Microaspiration occurs when there is distal migration of microorganisms present in the secretions accumulated above the ETT cuff. Biofilm formation has been described as the development of a network of secretions and attached microorganisms that migrate along the ETT cuff polymer and inside the lumen, facilitating the transfer to the sterile bronchial tree. Therefore, our objective was to review the literature related to recent advances in ETT technologies regarding their impact on the control of microaspiration and biofilm formation in patients on MV, and the subsequent impact on VAP. ***CHEST 2012; 142(1):231–238***

Abbreviations: ETT = endotracheal tube; HVLP = high-volume low-pressure; MV = mechanical ventilation; PUC = polyurethane cuff; RR = relative risk; SSD = subglottic secretion drainage; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is a common complication in patients on mechanical ventilation (MV). Depending on the surveillance methods used for the diagnosis of VAP, the risk of this complication ranges from 1.2 to 8.5 cases per 1,000 ventilator-days (0.6%-4%).[1] VAP is associated with increased hospital length of stay, mortality, infections due to multidrug-resistant pathogens, and an attributable hospital cost of approximately $10,000 to $25,000.[2,3] Therefore, preventive measures that could impact the incidence of VAP in the ICU setting must be considered a priority, because they could improve the safety of patients in the ICU. Multiple interventions are used to prevent VAP; however, there is a growing interest in those interventions related to the endotracheal tube (ETT) as one of the main targets linked to VAP.[2,4] An ETT tube is considered one of the major risk factors for VAP, acting both as a reservoir for potential infecting microorganisms and as a bridge between the oropharyngeal environment and the sterile bronchoalveolar space by bypassing host defenses.[5,6] Moreover, the ETT alters the ability of the host to clear secretions by coughing, and keeps the epiglottis open, allowing the passage of secretions and fluids into the airways.

The two most important mechanisms implicated in the development of VAP are microaspiration and biofilm formation. Microaspiration occurs when there is distal migration of microorganisms present in the secretions accumulated above the ETT cuff.[7] Biofilm

Manuscript received September 21, 2011; revision accepted March 8, 2012.

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Funding/Support: Dr Restrepo was funded partially by the National Heart, Lung, and Blood Institute [K23HL096054].

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DOI: 10.1378/chest.11-2420

formation is the development of a network of secretions and attached microorganisms that migrate along the ETT cuff polymer and inside the lumen of the ETT, facilitating the transfer to the sterile bronchial tree.[5,6,8-10] Interventions directed at preventing microaspiration have focused on limiting the secretions that pass the ETT cuff, whether by removing the secretions via aspiration, optimizing the cuff pressure to keep the cuff constantly inflated, or changing the ETT cuff materials to prevent microchannel formation. There are also interventions focused on the prevention of biofilm formation. Therefore, our objective was to review the literature regarding the recent advances in ETT technology targeted at preventing VAP (Tables 1, 2).

Prevention of Microaspiration

Cuff Pressure

Oropharyngeal and GI secretions can accumulate in the subglottic space and account for further migration or microaspiration of secretions around the inflated ETT cuff.[7,11] A cuff pressure as high as 60 cm H_2O is needed to reach a tight airway seal. However, the downside of this approach is that high cuff pressures can result in injury to the tracheal mucosa after a prolonged period of time.[25] High-volume low-pressure (HVLP) ETT cuffs were developed to prevent tracheal mucosal damage if pressure is maintained below 30 cm H_2O, and also to prevent fluid leakage. HVLP cuffs can reach 1.5 to two times the normal tracheal diameter when fully inflated and provide a good airway seal when the cuff pressure is below 30 cm H_2O.[25] However, even when the pressure in the HVLP cuff is increased to 50 cm H_2O, aspiration of subglottic secretions can still occur through the development of channel formation because of folding in the cuff.[26,27] Secretions aspirated through the microchannels can eventually reach the lower respiratory tract and increase the risk of acquiring VAP.[26,27] It has been presumed that maintaining a cuff pressure that automatically adjusts to an adequate level may solve the problem.[28] However, a randomized controlled clinical trial that used continuous cuff pressure monitoring with continuous and constant cuff inflation of 20 cm H_2O showed no observed difference in VAP incidence when compared with routine care.[29] Rello et al[30] also evaluated the outcomes of cuff pressure on the incidence of VAP, reporting that a constant cuff pressure below 20 cm H_2O during the first 8 days of intubation was an independent risk factor for the development of VAP (relative risk [RR], 4.23; 95% CI, 1.12-15.92). Most recently, continuous cuff pressure monitoring has been associated with a decreased rate of VAP.[31] In this prospective study, 122 patients expected to be on MV for at least 48 h were randomized to continuous control of cuff pressure (n = 62) and routine care of ETT cuff pressure (n = 62). An ETT cuff pressure of 25 cm H_2O was the target for both groups, and the enzyme pepsin was measured to identify the presence of microaspiration of gastric contents in the tracheal secretions. No differences were reported in tracheal ischemia score between groups, but decreased microaspiration of gastric contents, tracheobronchial bacterial concentration, and VAP rate (9.8% vs 26.2%, $P = .003$) were observed in the intervention group.[31]

Cuff Material and Shape

New technologies developed for HVLP ETT cuffs using different cuff materials and shapes attempt to prevent microchannel formation. Initially, it was thought that the material used in the standard polyvinyl ETT cuffs was the cause of the microchannel formation.[32,33] A new cuff made of polyurethane material that has an ultrathin cuff membrane (thickness of 7 μm compared with a thickness of >50 μm in the conventional HVLP ETT) may prevent the formation of folds within the ETT cuff.[32] When compared with the conventional HVLP ETT (polyvinyl cuff), the new HVLP ETT with ultrathin polyurethane cuff (PUC) showed less fluid leakage when the cuff pressure was between 25 and 30 cm H_2O in an in vitro model.[32,34] In addition, studies in mechanically ventilated patients with ETT PUC have shown that a lower sealing pressure (8-12 cm H_2O) was needed to prevent air leakage and a reduction in VAP.[23,33] However, no cost-effectiveness data are available for ETT with polyvinyl cuff ($1) or PUC ($3-$4) in the prevention of VAP.

Other cuff technologic advances have changed the globular shape of the ETT cuff to a tapered or cylindrical design. Clinical and in vitro studies have shown ETT tapered-shaped cuffs to be associated with lower fluid leakage than ETT cylindrical-shaped cuffs.[34,35] Similarly, Poelaert et al[22] reported a reduction in the frequency of early postoperative pneumonia with polyurethane ETT tapered-shaped cuffs in a small population of patients undergoing cardiac surgery.

Subglottic Secretion Drainage

The subglottic secretion drainage (SSD) was designed to evacuate the secretions that accumulate on top of the cuff when a good seal is provided by the pressure and/or material or shape of ETT cuffs. Therefore, a method that intermittently or continuously suctions secretions in the subglottic area may decrease the aspiration risk and prevent VAP.[14,21] This system is known as SSD and consists of an ETT with a separate dorsal lumen port that opens above the ETT cuff, in

Table 1—*Characteristics in Included Trials*

Study/Year	Country	Population Studied	Type of Study	Intervention ETT	Control ETT	VAP Definition Outcomes
Vallés et al[11]/1995	Spain	Medical-surgical ICU patients on MV for > 72 h	Randomized controlled	SSD	Non-SSD	Clinical and microbiologic confirmation of VAP
Zhenq et al[12]/2008	China	Patients on MV for > 48 h	Retrospective controlled	SSD	Non-SSD	Clinical confirmation of VAP
Mahul et al[13]/1992	France	Medical-surgical ICU patients on MV for > 72 h	Randomized controlled	SSD	Non-SSD	Clinical and microbiologic confirmation of VAP
Bo et al[14]/2000	China	Surgical ICU patients on MV for > 72 h	Randomized controlled	SSD (CASS)	Non-SSD	Clinical and microbiologic confirmation of VAP
Kollef et al[15]/1999	United States	Cardiothoracic ICU patients on MV after cardiac surgery	Prospective randomized clinical	SSD (CASS)	Non-SSD	Clinical confirmation of VAP
Girou et al[16]/2004	France	Patients intubated for > 5 d	Randomized controlled	SSD (CASS)	Non-SSD	Clinical and microbiologic confirmation of VAP
Bouza et al[17]/2008	Spain	Patients with major heart surgery	Randomized controlled	SSD (CASS)	Non-SSD	Clinical and microbiologic confirmation of VAP
Yang et al[18]/2008	China	Patients on MV for > 48 h	Randomized controlled	SSD (CASS)	Non-CASS	Clinical confirmation of VAP
Smulders et al[19]/2002	The Netherlands	Medical-surgical ICU patients on MV for > 72 h	Randomized controlled	SSD (intermittent suction)	Non-SSD	Clinical confirmation of VAP
Lacherade et al[20]/2010	France	Patients on MV for > 48 h	Randomized controlled	SSD (intermittent suction)	Non-SSD	Clinical and microbiologic confirmation of VAP
Lorente et al[21]/2007	Spain	Patients on MV for > 24 h	Clinical randomized	SSD/tapered-shaped PU cuff (intermittent drainage)	Non-SSD PVC cuff	Clinical and microbiologic confirmation of VAP
Poelaert et al[22]/2008	Belgium	Postoperative cardiac surgery	Prospective single-blind randomized	Tapered-shaped PU cuff	PVC cuff	Clinical confirmation VAP
Miller et al[23]/2011	United States	Adults in ICU intubated	Observational	Cylindric PU cuff	PVC cuff	Clinical and microbiologic confirmation of VAP
Kollef et al[24]/2008	United States	Patients on MV for > 24 h	Prospective randomized single-blind controlled	Silver-coated cuff	Non-silver-coated PVC cuff	Clinical and microbiologic confirmation of VAP

CASS = continuous aspiration of subglottic secretions; ETT = endotracheal tube; MV = mechanical ventilation; PU = polyurethane; PVC = polyvinylchloride; SSD = subglottic secretion drainage; VAP = ventilator-associated pneumonia.

Table 2—*VAP Incidence in Included Trials*

Study/Year	Centers, No.	Total Patients, No.	Intervention ETT, No. (%) [Rate per 1,000 Vent-d]	Control ETT, No. (%) [Rate per 1,000 Vent-d]	*P* Value	Conclusions
Vallés et al[11]/1995	1	153	14/76 (18.4) [19.9]	25/77 (32.5) [39.6]	.07	Decreasing trend in NP
Zhenq et al[13]/2008	NA	61	9/30 (30)	16/31(51)	< .05	Decrease in VAP
Mahul et al[13]/1992	1	145	9/70 (12)	21/75 (29)	< .05	Decrease in NP
Bo et al[14]/2000	NA	68	35 (23)	33 (45)	< .05	Decrease in VAP
Kollef et al[15]/1999	1	343	8/160 (5) [34.5]	15/183 (8.2) [43.2]	.2	Delaying trend to VAP
Girou et al[16]/2004	1	18	5/8 (62)	6/10 (60)	.6	No modification of tracheal colonization by intervention and semirecumbent body position
Bouza et al[17]/2008	1	690	12/331 (3.6) [17.9]	19/359 (5.3) [27.6]	0.2	Decreasing trend in VAP
Yang et al[18]/2008	NA	91	12/48 (25)	20/43 (46.5)	.03	Decrease in VAP
Smulders et al[19]/2002	1	105	2/49 (4.1) [6.4]	10/56 (17.9) [21.3]	.02 < .001	Decrease in VAP
Lacherade et al[20]/2010	4	333	25/169 (14.8) [17]	42/164 (25.6) [34]	.002 .02	Decrease in VAP
Lorente et al[21]/2007	1	280	11/140 (7.9) [7.5]	31/140 (22.1) [19.9]	.001	Decrease in early- and late-onset VAP
Poelaert et al[22]/2008	1	134	15/67 (23)	28/67 (42)	.02	Decrease in VAP
Miller et al[23]/2011	1	135	21/7,545[a] [2.8]	43/8,678[a] [5.3]	< .03 .014	Decrease in VAP
Kollef et al[24]/2008	54	1,509	37/766 (4.8)	56/743 (7.5)	.03	Decrease in VAP

NA = not available; NP = nosocomial pneumonia; Vent-d = ventilator-days. See Table 1 for expansion of other abbreviations.
[a]Ventilator-days.

which a negative pressure is applied in order to aspirate the secretions. Some examples of this type of ETT design are the Hi-Lo Evac tube and the Seal Guard or Taper Guard (Covidien). The outcomes in VAP prevention with SSD are conflicting, with some studies showing reduction in VAP incidence,[12-14,19] others suggesting a prolongation of the period of time to the development of VAP,[11,13-15,19,36] and still others showing a lack of efficacy of SSD to reduce VAP[30] or airway colonization.[16]

The benefit of SSD has been reported in two recent meta-analyses.[7,37] Muscedere et al[37] evaluated 2,442 patients from 13 randomized controlled trials, showing a reduction of 50% in the risk of acquiring VAP (overall risk ratio, 0.55; 95% CI, 0.46-0.66; $P < .00001$) and possible reduction in duration of MV (−1.08 days; 95% CI, −2.04 to −0.12; $P = .03$) and ICU length of stay (−1.52 days; 95% CI, −2.94 to 0.11; $P = .03$), but no reduction in mortality. Identical VAP reduction findings were reported previously in a smaller meta-analysis by Dezfulian et al,[7] mainly by reduction of pneumonia during the first 5 to 7 days after intubation (summary risk ratio, 0.51; 95% CI, 0.37- 0.71). However, Rello et al[30] raised the concern that a mechanical failure of SSD was evident in one-third of patients, adding to the risk factors associated with the development of VAP. They hypothesized that SSD failure was related to blockage of the subglottic suction port secondary to suctioned tracheal mucosa, as observed under flexible bronchoscopy.[30,38]

Another concern related to the use of SSD was the possibility of developing tracheal injury, because of the proximity of the subglottic suction port to the tracheal mucosa, as suggested in animal studies.[39] However, the Hi-Lo Evac tubes decreased the space between the upper portion of the cuff and the suction port, in an attempt to limit the development of tracheal injury. Similarly, LowTrach tubes, which incorporate three suction ports close to the ETT cuff, may prevent aspiration and have less tracheal mucosa injury by avoiding continuous suctioning (multiple suction ports present). Nevertheless, this ETT has a higher cost and limited clinical data are available.[36]

Determining the best method for delivering SSD is still a matter of controversy. There is evidence that patients with signs of subglottic aspiration failure do not have increased mortality, prolonged duration of MV, or prolonged ICU or hospital stays.[11,15,19] The use of continuous SSD has been recommended for patients on MV for >72 h or for those undergoing major heart surgery.[7,17] Current guidelines recommend the use of SSD to reduce early- and late-onset VAP[2,4]; however, there is no difference in VAP reduction when comparing continuous (RR, 0.50; 95% CI, 0.37-0.66) and intermittent (RR, 0.59; 95% CI, 0.47-0.74) suction.[37] A risk-benefit analysis should be considered when making the decision about using either technique of SSD. Although lower risk of harm (eg, tracheal injury and so forth)[21] is theoretically possible with intermittent SSD, a direct comparison with continuous suction has not been done, and the optimal

technique remains unclear. We suggest that it is safer to use intermittent SSD, especially when used with an ETT cuff with one of the newer designs, such as tapered-cuff and PUC.[20,21]

Recently, a decrease in early- and late-onset VAP with the combination of SSD and ETT with PUC has been reported.[21] A limitation of this study was that it was not able to differentiate between the independent influence of SSD and the PUC on VAP incidence.

Regarding cost effectiveness, Shorr and O'Malley[40] evaluated the cost and outcomes of continuous subglottic suctioning ETT ($15) and conventional ETT ($1) in the reduction of VAP. A marginal cost savings of $4,992 was reported for the continuous subglottic suctioning ETT[40] (Table 3).

In summary, the possible advantages of the ETT PUC-SSD combination in VAP prevention could derive from (1) the properties of the ultrathin cuff to prevent both fold formation within the cuff and leakage of aspirated secretions when cuff pressure is maintained between 20 and 30 cm H_2O, and (2) the properties of SSD to prevent aspiration of secretions with a further decrease in early- and late-onset VAP.[2,4,7,17] Although these measures for VAP prevention hold promise, more data will be needed to evaluate outcomes, prior to making firm recommendations for their use.

Prevention of Biofilm Formation

Biofilm formation provides a protective environment against antimicrobial and host defenses once potential pathogenic microorganisms are encased within it.[5,6,8,10] At the time of endotracheal intubation, there is a risk of introducing oropharyngeal contents into the airway, and after a few hours of MV, colonization of the ETT by bacteria has been observed.[5,10,41] Adair et al[41] found that identical pathogens isolated from the lower respiratory tract and the ETT were associated with the development of VAP in 70% of cases. The presence of microorganisms on the ETT cuff may occur as a consequence of contaminated oropharyngeal contents or gastric secretion reflux. Once microorganisms reach the ETT, they can adhere to the surface and produce biofilm for protection and proliferation. The inadequate inhibitory concentration of antimicrobial drugs sometimes found in the airways may favor this adherence.[41] Other risk factors associated with the development of VAP include chronic pulmonary disease, duration of MV, sepsis, RBC transfusion, acute respiratory distress, neurologic disorders, and prior use of antibiotics.[4] Several new ETT technologies have tested the incorporation of antibiotics into biomaterials, showing a possible decrease in lung colonization by pathogenic bacteria.[42-47] Although long-term use of antimicrobial-impregnated central venous catheters has shown no selection of bacterial resistance,[48] biofilm formation has been associated with antibiotic-resistant pathogens and lack of antimicrobial penetrability into the biofilm of the ETT.[41,49,50] Recently, an in vitro model evaluated the role of antimicrobial photodynamic therapy in the reduction of ETT biofilm.[51] This photodynamic therapy consists of spraying a small amount of photosensitizer solution (methylene blue) into the ETT lumen, which is exposed to light (664 nm) through a small optical fiber located within it. This study demonstrated a reduction in the polymicrobial biofilm ($>99.9\%$, $P<.05$) after a single treatment.[51] However, more data are needed before implementing antimicrobial photodynamic therapy in clinical practice.

Silver-coated ETTs have emerged as a viable alternative, after the success shown in other materials and tubes, such as urinary catheters.[52] Silver has a very effective broad-spectrum antimicrobial activity, decreases bacterial adhesion in vitro, and blocks biofilm formation in animal models.[43,44,53] In animals, silver coating of the ETT delayed the colonization on the inner tube surface, reduced the severity of lung colonization, and decreased histopathologically defined pneumonia.[46] In humans, a small randomized study demonstrated a decreased burden of bacterial airway colonization.[47] In this study, the silver-coated ETT was composed of silver ions microdispersed in a proprietary polymer over both the inner and outer lumens, providing a sustained antimicrobial effect, and was well tolerated.

A randomized phase I-II clinical trial that focused on biofilm prevention in cardiac surgery patients on

Table 3—*Endotracheal Tube Cost-effectiveness and VAP*

Study	ETT Cuff	Cost, $	Baseline Prevalence of VAP, %	RR Reduction, %	Savings Cost for a Case of VAP Prevented,[a] $	Cost for a Case of VAP,[a] $
Shorr et al[3]	Silver coated	90	9.7	24	12,840	16,620
Shorr and O'Malley[40]	CASS	15	25	30	4,992	5,365[b]

RR = relative risk. See Table 1 for expansion of other abbreviations.

[a]Marginal costs (±).

[b]May have underestimated the true cost of VAP.

MV for 12 to 24 h showed that silver sulfadiazine in polyurethane ETT can be used easily and safely and prevented colonization of the ETT lumen (number needed to treat = 2.8).[45] Most recently, a large, randomized, multicenter study demonstrated a decrease in microbiologically proven VAP incidence in patients intubated with the silver-coated ETT, when compared with a standard ETT.[24] The study performed at 54 centers in the United States in 1,509 patients who required MV for more than 24 h showed a lower rate of microbiologically confirmed VAP of 4.8% (37 of 766 patients) in the group randomized to the silver-coated ETT compared with 7.5% (56 of 743 patients) in the group randomized to an uncoated ETT ($P = .03$, number needed to treat = 37). In addition, the silver-coated ETT delayed the occurrence of VAP ($P = .005$). However, no differences were observed in duration of MV or in length of stay in the ICU or the hospital. According to worldwide observational data, most patients require < 10 days of MV; thus, delaying the occurrence of VAP may have important clinical implications, such as cost.[54] In addition, if there are strategies focused on extubating the patients earlier, there will be less chance of developing VAP. These results suggest once again that controlling bacterial colonization and biofilm formation may decrease the incidence of VAP.[24] The cost of the coated ETT compared with the conventional ETT is higher ($90 vs $2, respectively), but Shorr et al[3] found the coated ETT to be more cost effective in the prevention of VAP, with cost savings of $12,840 per case of VAP prevented (95% CI, $9,630-$16,356) (Table 3).

Finally, mechanical removal of biofilm has been proposed with the use of the mucus shaver.[55-57] This device is an inflatable silicone rubber that is introduced into the ETT lumen for extraction or "shaving" of material accumulated within the ETT. Its efficacy and safety have been shown in animal models and more recently in a prospective randomized trial.[55-57] Berra et al[57] randomized 24 patients to receive standard ETT suctioning or standard ETT suctioning plus the mucus shaver device. Upon extubation, an ETT internal bacterial colonization of 8% in the mucus shaver group vs 83% in the control group was observed (n = 24, $P < .001$). Although no adverse events were found related to the mucus shaver, more clinical trials will be needed to evaluate the effectiveness of this device.

Combinations of coating materials have been tested with limited clinical data. Chlorhexidine as a topical application has emerged as a safe and effective alternative for oral care in the critically ill.[2,58] This agent has been tested in combination with sulfadiazine in a PUC-ETT in mechanically ventilated sheep. This study showed a suppression of tracheal colonization in the coated ETT group, whereas heavy colonization was seen in the control group.[44] To our knowledge, there are no human studies using this preventive measure, to date.

Others agents, such us "gendine," a combination of gentian violet and chlorhexidine, have broad-spectrum antimicrobial activity and have been evaluated in vitro in ETT. Prolonged antimicrobial durability, elimination of adherence of frequent nosocomial pathogens, and no significant changes in bacterial resistance have been reported.[50,59] However, clinical trials will be needed to evaluate the effectiveness of coating materials such as chlorhexidine in ETT colonization and infection reduction.[59]

Conclusions

ETT cuff colonization by bacterial pathogens and biofilm formation are the proposed mechanisms for the pathogenesis of VAP. There is current evidence that reducing these mechanisms may effectively aid in the prevention of VAP, which results in an important morbidity and health care cost impact. New ETT technologies have been designed to take advantage of this success and, among them, the SSD-ETT cuff appears to be safe and cost effective in VAP prevention. Other new ETT cuffs technologies have also shown beneficial effects in VAP prevention, but more data are needed to corroborate these. Some of these technologies have focused on changing ETT cuff material (polyurethane), shape (eg, cylindrical, tapered), and monitoring pressure devices for a more effective sealing, whereas others have attempted to prevent biofilm formation (silver coating, mucus shaver, photodynamic therapy). Unfortunately, limited cost-effectiveness data are available for these later novel ETTs, except for silver-coated ETT, which appears to be cost effective in VAP prevention. The decision to implement an expensive new ETT strategy requires not only assessing the cost-effective properties of the strategy, but also incorporating the incidence of VAP at the institution and complying with less expensive and available interventions such as semirecumbency.

It is important to note that decreasing the incidence of VAP requires the incorporation of multiple interventions at the same time in bundles, because single interventions have not been shown to be successful. Therefore, further research focused on ETT strategies that may add to current pharmacologic and nonpharmacologic strategies may contribute to the prevention of VAP in clinical practice.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Restrepo participated on advisory boards for Janssen Pharmaceuticals, Inc;

Theravance; Forest Laboratories; Johnson & Johnson; and Novartis AG. He is a former speaker for Covidien; C. R. Bard, Inc; Johnson & Johnson (Ortho-McNeil-Janssen); and Pfizer, Inc; and is a consultant for Theravance and Pfizer, Inc (Wyeth). Drs Fernandez and Levine have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute. The funding agencies had no role in the preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the University of Texas Health Science Center at San Antonio.

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