and less-carried serotypes such as serotype 1 or 3 elicit similar results, and would it be safe?

So is eradication of *S. pneumoniae* colonization good or bad? This is not an easy question to answer. From the point of view of prevention, if colonization is a precursor to invasive disease, then eradication of colonization makes sense. But because nasopharyngeal colonization is a dynamic process where multiple species compete for the same niche, evicting the pneumococcus from its natural habitat may have unintended consequences. Regev-Yochay and colleagues found that pneumococcal carriage in children, especially of PCV7 vaccine serotypes, protected against *Staphylococcus aureus* carriage (20). Similarly, in animal models, other bacterial species have been shown to compete to establish colonization (10). And as carriage is immunogenic, is tampering with the nasal environment a wise thing?

Author disclosures are available with the text of this article at www.atsjournals.org.

Blanca E. Gonzalez, M.D.
Case Western Reserve University Lerner School of Medicine
Cleveland, Ohio
and
Children's Hospital Center for Pediatric Infectious Diseases
Cleveland Clinic Foundation
Cleveland, Ohio

Michael R. Jacobs, M.D., Ph.D.
Department of Pathology
Case Western Reserve University School of Medicine
Cleveland, Ohio
and
University Hospitals Case Medical Center
Cleveland, Ohio

References

1. Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, Reingold A, Thomas A, Schaffner W, Craig AS, *et al.*; Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201:32–41.
2. Poehling KA, Talbot TR, Griffin MR, Craig AS, Whitney CG, Zell E, Lexau CA, Thomas AR, Harrison LH, Reingold AL, *et al.* Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 2006;295:1668–1674.
3. Kaplan SL, Barson WJ, Lin PL, Stovall SH, Bradley JS, Tan TQ, Hoffman JA, Givner LB, Mason EO Jr. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. *Pediatrics* 2010;125:429–436.
4. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012;61:816–819.
5. Musher DM. Editorial commentary: should 13-valent protein-conjugate pneumococcal vaccine be used routinely in adults? *Clin Infect Dis* 2012;55:265–267.
6. Musher DM, Sampath R, Rodriguez-Barradas MC. The potential role for protein-conjugate pneumococcal vaccine in adults: what is the supporting evidence? *Clin Infect Dis* 2011;52:633–640.
7. Ridda I, Musher DM. Is there a potential role for protein-conjugate pneumococcal vaccine in older adults? *Australas Med J* 2012;5:231–235.
8. McCool TL, Cate TR, Moy G, Weiser JN. The immune response to pneumococcal proteins during experimental human carriage. *J Exp Med* 2002;195:359–365.
9. Ferreira DM, Neill DR, Bangert M, Gritzfeld JF, Green N, Wright AKA, Pennington SH, Bricio Moreno L, Moreno AT, Miyaji EN, *et al.* Controlled human infection and rechallenge with *Streptococcus pneumoniae* reveals the protective efficacy of carriage in healthy adults. *Am J Respir Crit Care Med* 2013;187:855–864.
10. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4: 144–154.
11. Briles DE, Ades E, Paton JC, Sampson JS, Carlone GM, Huebner RC, Virolainen A, Swiatlo E, Hollingshead SK. Intranasal immunization of mice with a mixture of the pneumococcal proteins PsaA and PspA is highly protective against nasopharyngeal carriage of Streptococcus pneumoniae. *Infect Immun* 2000;68:796–800.
12. Lebon A, Verkaik NJ, Labout JA, de Vogel CP, Hooijkaas H, Verbrugh HA, van Wamel WJ, Jaddoe VW, Hofman A, Hermans PW, *et al.* Natural antibodies against several pneumococcal virulence proteins in children during the pre-pneumococcal-vaccine era: the generation R study. *Infect Immun* 2011;79:1680–1687.
13. Hausdorff WP, Hoet B, Schuerman L. Do pneumococcal conjugate vaccines provide any cross-protection against serotype 19A? *BMC Pediatr* 2010;10:4.
14. Hulten KG, Kaplan SL, Lamberth LB, Barson WJ, Romero JR, Lin PL, Bradley JS, Givner LB, Tan TQ, Hoffman JA, Mason EO. Changes in pediatric Streptococcus pneumoniae serotype 19A invasive infections in children from 1993 to 2011. *J Clin Microbiol* 2013:1294–1297.
15. Oliveira ML, Miyaji EN, Ferreira DM, Moreno AT, Ferreira PC, Lima FA, Santos FL, Sakauchi MA, Takata CS, Higashi HG, *et al.* Combination of pneumococcal surface protein A (PspA) with whole cell pertussis vaccine increases protection against pneumococcal challenge in mice. *PLoS ONE* 2010;5:e10863.
16. Moreno AT, Oliveira ML, Ferreira DM, Ho PL, Darrieux M, Leite LC, Ferreira JM Jr, Pimenta FC, Andrade AL, Miyaji EN. Immunization of mice with single PspA fragments induces antibodies capable of mediating complement deposition on different pneumococcal strains and cross-protection. *Clin Vaccine Immunol* 2010; 17:439–446.
17. Malley R, Anderson PW. Serotype-independent pneumococcal experimental vaccines that induce cellular as well as humoral immunity. *Proc Natl Acad Sci USA* 2012;109:3623–3627.
18. Wright AK, Ferreira DM, Gritzfeld JF, Wright AD, Armitage K, Jambo KC, Bate E, El Batrawy S, Collins A, Gordon SB. Human nasal challenge with Streptococcus pneumoniae is immunising in the absence of carriage. *PLoS Pathog* 2012;8:e1002622.
19. Moffitt KL, Gierahn TM, Lu YJ, Gouveia P, Alderson M, Flechtner JB, Higgins DE, Malley R. T(H)17-based vaccine design for prevention of Streptococcus pneumoniae colonization. *Cell Host Microbe* 2011;9: 158–165.
20. Regev-Yochay G, Dagan R, Raz M, Carmeli Y, Shainberg B, Derazne E, Rahav G, Rubinstein E. Association between carriage of Streptococcus pneumoniae and Staphylococcus aureus in children. *JAMA* 2004;292:716–720.

DOI: 10.1164/rccm.201302-0361ED

Continuous Positive Airway Pressure versus the Mandibular Advancing Splint

Are They Equally Effective in Obstructive Sleep Apnea Management?

For many years, continuous positive airway pressure (CPAP) has been considered the standard of care for patients with obstructive sleep apnea (OSA), with all other therapies being relegated to patients who fail CPAP, with CPAP failure being most commonly due to poor acceptance or adherence. In this issue of the *Journal*, Phillips and colleagues (pp. 879–887) present

a randomized crossover trial of CPAP versus a mandibular advancing splint (MAS) in a large group of patients with mild to severe OSA (1). The primary outcomes were mean 24-hour blood pressure, subjective device compliance, quality of life, subjective sleepiness, driving performance, apnea–hypopnea index (AHI) per full in-lab polysomnography, and therapy preference after 1 month of treatment with each device. They report largely similar outcomes in most domains for the two therapies with better compliance and slightly greater improvements in quality of life with the MAS. On the other hand, CPAP yielded a significantly lower AHI. Thus, two questions must emerge: (*1*) What is different about this study from previous ones? and (*2*) How should this affect the approach to care of OSA patients?

This study is different from all previous comparisons of CPAP versus MAS (2–4) in a number of important ways. These include:

- The size of the study, with the 108 patients completing both arms of the study being substantially larger than all previous protocols
- The breadth of the outcomes assessed as outlined above
- The careful randomization of both initial exposure to the therapies and their implementation
- The inclusion of patients with all severities of OSA
- The comparative effectiveness approach used in the comparison of the two devices

There are a few minor weaknesses as well. The study was powered to detect a change in blood pressure, which seems a poor choice based on the highly variable and often minimal effect of any OSA therapy on systemic blood pressure. The assessment of compliance with both therapies was subjective, although some objective data are provided for CPAP. This was the result of the obvious difficulty in obtaining accurate, objective usage data for the MAS. Finally, sleepiness was only subjectively assessed, whereas an objective measure might have been more interesting. However, these are only minor problems in an otherwise well-designed, important study.

The much harder question is how should these data influence how we care for patients with OSA? One answer would be that all OSA patients, regardless of severity, should initially be offered both options and be allowed to choose between the two, based on personal preference. However, there are potential problems with this approach, which will be addressed for each device separately. In the case of the MAS, not all patients responded similarly to the device. Although individual data were not provided in the paper, in patients with severe OSA the mean residual AHI during MAS therapy (intention to treat results) was about 18–19. As a result, many of these patients must have had a residual AHI greater than 20, which is not a particularly satisfactory result. Thus, just because the overall outcomes for the groups were similar does not indicate that each therapy produced a comparable or acceptable outcome for each patient. For patients on the MAS with an AHI of more than 20 (or >30 if that is a more appropriate threshold), particularly those with some residual symptoms, other therapeutic options would have to be considered. Thus, the MAS device must be fabricated and tested in each patient (or certainly in patients with severe OSA) before it can be assumed to be adequate therapy. This is currently an expensive proposition, as the cost of MAS fabrication in the United States is between $1,500 and $2,000, with a home sleep test costing about $250–300. Thus, we desperately need a method to quantify MAS effectiveness short of making the device for each patient and then determining if it works.

CPAP has its own well-known problems, generally poor acceptance and adherence. Thus, despite very high success rates, acceptable long-term use is probably less than 50% (5, 6). However, CPAP acceptance or rejection generally occurs fairly rapidly after its introduction, which should allow for a relatively quick assessment of whether CPAP will be tolerable in a given patient (7). To continue trying to improve CPAP use in a noncompliant patient after 2–3 months of failed efforts is largely futile, although we all know of a few patients in which this has worked. Thus, after 2–3 months of such efforts, other therapies should be strongly considered in the nonadherent patient.

Thus, an overall scheme might be to offer all patients with mild to moderate OSA the choice between CPAP and MAS. If CPAP use is acceptable, it can be continued. If symptoms are adequately alleviated with the MAS, no further testing is probably required, as mean AHIs in these groups on a MAS in this study (1) were about 4 and 8 for mild and moderate OSA patients, respectively. If either fails to achieve this endpoint, the other therapy could be considered. Severe OSA patients may be a bit different due to a relatively high failure rate with the MAS, although the exact percentage of failures was not provided in this paper and will certainly vary depending on the failure threshold selected. In this severe group, a 1- to 2-month trial of auto-PAP might be the better (and certainly cheaper) initial approach and, if usage is adequate, the PAP could be continued. If auto-PAP proves unacceptable, other therapies, including MAS, would have to be considered.

The real problem, as suggested above, is our current inability to determine if a MAS device will work in a given patient short of fabricating a custom device and testing it. Two solutions have been proposed. In one, a temporary, inexpensive device can be produced for a given patient and mechanically advanced during a sleep study to determine efficacy (8, 9). If it is efficacious, a custom device could be fabricated and used by the patient. The other possible solution is the use of an adjustable boil-and-bite device that is again relatively inexpensive and could be advanced gradually over days to weeks by the patient or the physician/dentist to the maximum tolerable position. A sleep study could then be conducted in the home or lab, and based on the results of this study, decisions could be made as to whether a custom oral appliance is an appropriate therapeutic choice. Neither approach has been adequately tested, and they must be before broad acceptance would be reasonable. Until this happens, CPAP may remain the initial therapy in patients with severe OSA.

Author disclosures are available with the text of this article at www.atsjournals.org.

David P. White, M.D.
Division of Sleep Medicine
Brigham and Women's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

References

1. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA, *et al.* Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2013;187:879–887.
2. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;170:656–664.
3. Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive

airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996;109:1269–1275.
4. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 2002;166:855–859.
5. Dinges DF, Kribbs NB, Schwartz AR, Smith PL, Pack AI. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1993;147:887–895.
6. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15:343–356.
7. Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, Smith PL, Schwartz AR, Schubert NM, Gillen KA, *et al*. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep* 1997; 20:278–283.
8. Tsai WH, Vazquez JC, Oshima T, Dort L, Roycroft B, Lowe AA, Hajduk E, Remmers JE. Remotely controlled mandibular positioner predicts efficacy of oral appliances in sleep apnea. *Am J Respir Crit Care Med* 2004;170:366–370.
9. Dort LC, Hadjuk E, Remmers JE. Mandibular advancement and obstructive sleep apnoea: a method for determining effective mandibular protrusion. *Eur Respir J* 2006;27:1003–1009.

DOI: 10.1164/rccm.201302-0318ED