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Technological and behavioral strategies to reduce treatment burden and improve adherence to inhaled antibiotics in cystic fibrosis

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Summary
Aerosolized antibiotics are a common treatment option for patients with cystic fibrosis and chronic airway infection, as high doses can be delivered topically to the site of the infection while systemic exposure is minimized. Patients also use other aerosolized therapies (e.g. mucus-active agents, airway-wetting agents, and bronchodilators), adding significantly increase timed and complexity to their daily regimen, and often leading to lower adherence rates. A number of novel technological strategies are available that may reduce dose frequency and increase the speed of drug delivery. Psychologically based therapies may also be used to help modify behavior and thus improve adherence to treatment. Clinicians need to explore both technological and psychological strategies that will assist in the successful maintenance of treatment requirements.

Introduction

Cystic fibrosis (CF) lung disease is characterized by endobronchial infection, excessive inflammation, progressive airway obstruction, bronchiectasis, and eventual respiratory failure.[1] Although multiple species of opportunistic microbes can be found in the airways of patients with CF, *Pseudomonas aeruginosa* is the most prevalent and is associated with poor outcomes.[2,3] Thus, treatment guidelines emphasize the use of inhaled antimicrobials for suppression of chronic *P. aeruginosa* infection,[4,5] as well as for eradication of early infection.[5] Although they have not been well studied for the treatment of pulmonary exacerbations, inhaled antibiotics are commonly used to help manage such exacerbations.[6] Because infection is localized to the endobronchial space in patients with CF, aerosolized antibiotics are an attractive option, since high doses are delivered topically to the site of infection while systemic exposure is minimized.[7] Currently, widely inhaled antibiotic treatments available as nebulizer solutions include tobramycin inhalation solution (TIS; TOBI®; Novartis Pharmaceuticals, East Hanover, NJ, USA; and Bramitob®; Chiesi Farmaceutici S.p.A., Parma, Italy) and aztreonam lysine for inhalation solution (AZLI; Cayston®, Gilead Sciences, Forest City, CA, USA), whereas colistimethate sodium (Colomycin®; Forest Laboratories UK Ltd, London, England, UK; and Promixin®; Profile Pharma Limited, Chichester, West Sussex, UK) is approved for use in only a few European countries. In addition to aerosolized antibiotics, patients with CF often use several other inhaled therapies, including bronchodilators, mucus-active agents, and airway-wetting agents. The addition of numerous aerosol treatments to airway clearance maneuvers means a treatment burden in excess of 2 hours per day for many individuals with CF.[8] As observed with other chronic illnesses, both the time and the complexity of a medical regimen are associated with low adherence rates,[9] and there is no reason to think that this is any different with CF.

Studies of patients with CF estimate significant rates of nonadherence from 20% to 70%, with rates varying according to the scale used, the content, and the rater.[10,11] Adherence rates vary for different aspects of therapy, with the best rates for medication and the poorest for

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diet and physiotherapy.[12] Adherence estimates for inhaled antibiotics range between 31% and 53%.[13] Low rates of adherence to chronic medications are associated with poor disease control, absenteeism, and increased exacerbations in patients with asthma.[14,15] Data relating adherence to patient outcomes were lacking in the field of CF until very recently. Using pharmacy refill records to assess adherence, Eakin and colleagues found that nonadherence to chronic pulmonary medications predicted the need for intravenous (IV) antibiotics and was also associated with lower baseline lung function.[13] Using a large database of health care claims, Briesacher and associates reported poor overall adherence with TIS, with only 7% of patients who were prescribed TIS receiving $\geqslant$4 treatment cycles in 1 year.[16] This study demonstrated a 60% decrease in the risk for hospitalization in those patients who were adherent to their treatment regimen. Thus, we now have evidence that demonstrates a relationship between low usage of chronic medications (including inhaled antibiotics) and increased exacerbations requiring IV therapy. Improving patient outcomes rests, in part, on increasing adherence to chronic therapies.

Since a large part of the adherence problem among the CF population may relate to the significant time burden associated with the use of inhaled therapies (including reconstituting the drug, preparing the nebulizer, and cleaning/disinfecting procedures), it seems logical that strategies for minimizing the time may improve patient adherence rates. Recent innovations in aerosol formulations and devices have been associated with improved delivery efficiency, better airway deposition, and significant reductions in time burden.[17] We cannot assume that reduction in administration time alone, however, will solve the adherence dilemma. Asthma medications take only a few seconds to administer via a metered-dose inhaler (MDI) or dry powder inhaler (DPI), yet adherence rates are low. Therefore, we also need to consider and incorporate behavioral and psychotherapeutic approaches into the treatment paradigm, in order to make certain that persons with CF achieve optimal outcomes. This paper will review both the technological and the behavioral aspects of reducing the treatment burden and improving adherence among patients with CF.

Variables to consider with the use of inhaled antibiotics

Strategies that can significantly reduce treatment burden include reducing the dosing frequency, increasing the speed of drug delivery, and simplifying device cleaning regimens. As with any inhaled agent, the aerosol variables of particle size and velocity need to be considered, as well as such patient variables as age, upper and lower airway size, disease severity, and suitability of the device for the individual.[18]

The pharmacokinetics (PK) and pharmacodynamics (PD) of the various antimicrobial agents must be taken into consideration when dosing regimens are designed. Aminoglycosides and fluoroquinolones work by concentration-dependent killing: the ratio of the maximum drug concentration (C_{max}) or area under the curve (AUC) vs the minimum inhibitory concentration (MIC) of the organism.[19] Beta-lactam antibiotics demonstrate time-dependent killing – that is, the longer the concentration remains above the MIC of the organism, the better the effect. Aminoglycoside activity is inhibited by sputum,[19] and bacteria in biofilms are protected from antibiotic activity.[20] The main strategy for managing these challenges is to use very high topical doses to account for the huge variability in patient characteristics, bacterial sensitivity to antibiotics, and PK/PD parameters. The loading doses in aerosol delivery devices range from tens to hundreds of milligrams of drug per dose. To improve delivery, one can consider optimization of formulations, the delivery devices, or both.

Formulation strategies

One strategy for reducing the time of administration is to concentrate the drug formulation. TIS (TOBI) was approved as a 60 mg/mL formulation, with each 300 mg dose taking approximately 15 to 20 minutes to nebulize with a PARI LC® Plus Jet Nebulizer (PARI Respiratory Equipment Inc., Midlothian, Virginia, USA).[21] A more concentrated formulation (75 mg/mL) of TIS (Bramitob) reduces dosing time to about 12 minutes using the same nebulizer.[22] Combining increased concentration (100 mg/mL) with a faster delivery device – an efficient eFlow® Electronic Nebulizer (PARI GmbH, Starnberg, Germany) – decreases the delivery time to 4 minutes.[23] There is likely an upper limit for the maximum concentration of inhaled antibiotics, with the limiting factors being the capacity to nebulize the concentrated drug, as well as the ability of patients to tolerate highly concentrated formulations.

Increasing the residence time of the drug in the lung can reduce the dosing frequency needed for inhaled antibiotics. Liposomes have been used to slow the release of drugs, resulting in a time-release effect in the lung. Although this approach may result in a lower initial C_{max}, it increases the AUC (which is important with fluoroquinolone use). Unfortunately, formulations of liposomal beta-lactams are not very stable. Aerosol antibiotics under investigation using liposomal formulations include amikacin[24,25] and ciprofloxacin.[26]

One of the most convenient forms of inhalation technology is the DPI, which is used commonly for patients with asthma and/or chronic obstructive pulmonary disease. DPIs are small and portable, are associated with rapid drug delivery times, and require no special cleaning or disinfection procedures, thus saving patients even more time. Since several milligrams of antibiotic need to be deposited in the lungs, however, more efficient technology is required than simple milled powders delivered by a typical DPI. Milled powders are often blended with lactose to help overcome strong interparticle forces, reducing the amount of active drug that can be delivered per dose. Newer engineered powders have been developed to reduce the need for excipients and improve deaggregation of the powders into small particles upon inhalation. One spray-drying technique was used to develop a DPI formulation of colistimethate (Colobreathe®, Forest Laboratories UK Ltd., London, England, UK)), which is currently under investigation.[27]

Another new generation of engineered powder particles called PulmoSphere® (Nektar Therapeutics, San Carlos, CA, USA) was developed for systemic or topical airway targets.[28]

Low-density, spherical particles are created by spray drying an emulsion of perfluorocarbons, water, and the compound. The resulting particles are low-density, porous, and have reduced interparticle cohesion, thus allowing release of the drug from a punctured capsule with lower flow rates than with typical dry powder formulations. Pulmonary deposition is higher with these engineered powders vs. classic DPIs.[29] Tobramycin inhalation powder (TIP; TOBI® Podhaler®, Novartis Pharmaceuticals, Basel, Switzerland) was developed using the PulmoSphere technology to reduce the patient time burden associated with administration of TIS. Deposition studies in healthy volunteers demonstrated similar distribution of the drug in the airways with TIP vs TIS.[29] A study of patients with CF showed that TIP 112 mg divided into 4 capsules approximated the PK characteristics of TIS 300 mg aerosolized with the PARI LC Plus nebulizer.[30] Phase 3 studies subsequently demonstrated the effectiveness of TIP vs. placebo,[31] as well as similar safety and efficacy of TIP compared with TIS when administered over 3 month-on, month-off cycles.[32] Patients rated TIP as more convenient than TIS, and administration time averaged 5.6 vs 19.7 minutes, respectively, with no cleaning rituals required with TIP.[32] TIP was recently approved for use in Europe, Canada, and some South American countries. Inhaled ciprofloxacin using this technology is under investigation.[33] A minimum required lung volume and airflow are still required to activate the DPI, so use is limited to patients $\geqslant$6 years of age.[34]

Finally, combining more than one antibiotic into a single formulation may be effective for improved killing of *P. aeruginosa* or targeting other pathogens. A recent phase 2 study of a liquid formulation of fosfomycin and tobramycin, combined and delivered by an efficient eFlow nebulizer, showed improved clinical outcomes and reduced sputum density of *P. aeruginosa* and *Staphylococcus aureus*, including the methicillin-resistant strain.[35] It is even technically feasible to combine drugs with different functions, such as mucus-active agents and antibiotics, in dry powder formulations.[36] Although that particular strategy may seem counterintuitive, it raises the interesting question of whether inhaled therapies for patients with CF can or should be combined to reduce the treatment burden and improve adherence.

Aerosol device technology

The high doses of inhaled antibiotics needed to achieve adequate levels in the lungs are beyond the capability of most asthma drug delivery systems, including MDIs, multidose DPIs, and soft-mist inhalers. Besides the aforementioned dry powder technology, wet nebulizers can also deliver high doses of medication to the respiratory tract.

Traditionally, jet nebulizers have been used for delivery of high-payload drugs. These devices are fairly ubiquitous, as other CF agents (dornase alfa, hypertonic saline) utilize this technology. Patients of any age can use jet nebulizers, including infants and young children; however, jet nebulizers are associated with long nebulization times, high residual doses, and arduous cleaning and disinfection procedures to reduce cross infection. Currently, jet nebulizers are used to deliver the two approved liquid formulations of tobramycin and the investigational liposomal ciprofloxacin.

A new generation of aerosol delivery systems has been developed that use a vibrating, perforated mesh to generate the droplets. These devices are portable, silent, do not require compressed air, and can operate with batteries or alternating current. The device housing can be designed to minimize residual dose and drug waste. The particle size of the aerosol that is produced depends on the size of the mesh holes and on the drug formulation properties. Importantly, vibrating mesh nebulizers are much faster than jet nebulizers at nebulizing the same volume.[17,18]

One drawback to these devices is a tendency for the tiny holes of the mesh to clog over time. Some solutions may be too viscous to pass through a mesh system. Also, with repeated use, the nebulization time can gradually increase. Periodic replacement of the mesh is required to maintain optimal operation. Finally, these devices still require cleaning and disinfection, and the mesh has to be handled carefully to avoid damage.

The eFlow Electronic Nebulizer contains a vibrating mesh platform that can be customized for different formulations. The medication cup is sloped so that the fluid is guided to the perforated mesh, thus minimizing the residual volume. An aerosol chamber conserves the drug during exhalation, and a mouthpiece with a 1-way valve directs exhaled air away from the nebulizer. The eFlow nebulizer was used early in the development of AZLI, to reduce each treatment time to 2 to 3 minutes.[37] Customized versions of the eFlow device are also being used for clinical development with inhaled levofloxacin (Aeroqin™ [MP-376], Mpex Pharmaceuticals, San Diego, CA, USA; 4 to 6 minutes per treatment),[38] liposomal amikacin (12 to 15 minutes per treatment), and the fosfomycin-tobramycin combination.

In addition to the customized eFlow nebulizer for formulations in development, an "open" device was designed to mimic the particle size and efficiency of the PARI LC Plus Jet Nebulizer. The eFlow Rapid has a similar residual dose and particle size as the LC Plus, and a smaller aerosol chamber than the custom eFlow devices. Studies of this device using TIS in patients with CF revealed higher sputum levels than with the LC Plus,[39] but lower deposition measured by scintigraphy (reduced by 41%).[40] Nevertheless, the eFlow Rapid is used widely in Europe for such CF medications as TIS, hypertonic saline, and dornase alpha. A highly efficient version of the eFlow ((PARI Respiratory Equipment Inc., Midlothian, Virginia, USA)) was introduced in the United States as an open device for CF agents and, more specifically, for such compounded antibiotics as tobramycin and colistin. This device delivers medication faster than a jet nebulizer, with 2 to 4 times the predicted drug delivery to the lung.[17] Therefore, extreme caution must be used when delivering medications off label with the eFlow Trio, in order to avoid side effects and toxicity.

Newer aerosol delivery systems, called "smart devices," can time the release of aerosol to a specific portion of inhalation and/or guide the patient to inhale very slowly to maximize lung deposition. The I-neb Adaptive Aerosol Delivery (AAD) device (Philips Respironics, Chichester, West Sussex, UK) contains a vibrating horn with stationary mesh and incorporates software that monitors patient breathing patterns.[41] This device adapts to changes in breathing pattern and releases aerosol during the first 50% to 80% of inspiration, thus conserving drug during exhalation. The I-neb can be operated either in the tidal breathing

mode (TBM) or in the targeted inhalation mode (TIM), the latter of which coaches patients to perform slow, deep inhalations to maximize aerosol deposition. The I-neb utilizes auditory, visual, and tactile feedback to alert patients about proper use of the device, and to signal that their treatment is complete. The benefits of the TIM mode are that (1) controlled inspiration can reduce the wide variability between subjects for aerosol deposition[42] and (2) it shortens the duration of treatment. In a recent study, the I-neb operated in TIM was associated with a shorter mean treatment time (3.7 minutes) vs. TBM (6.9 minutes) with inhaled colistin.[43] Mean adherence was also maintained in the TIM group but declined slightly in the TBM group. The I-neb is approved for use with colistin (Promixin) in the UK and is often used off label with other CF medications.

The AKITA$^{2®}$ (Activaero GmbH, Gautling, Germany) is another device that limits inspiratory flow and incorporates vibrating mesh technology to optimize aerosol delivery to the lungs. This device uses a SMART CARD that stores a patient's lung function and instructs the device when to pulse the aerosol during inspiration, thus making it possible to target proximal or distal airways.[44] The AKITA supplies air from a compressor, so that the patient inhales at a constant, slow rate of 12 to 15 liters per minute, resulting in decreased variability in deposition. As with the I-neb, the prolonged inspiratory phase associated with use of the AKITA also reduces the time of administration for inhaled drugs. By controlling the breathing pattern with devices such as the I-neb and the AKITA, aerosol deposition is higher, distribution in the airways is more uniform, variability is reduced, and treatment time is shortened.

Monitoring adherence with technology

Innovations in nebulizer technology include not only improving the aerosol performance of the device, but also allowing for the recording of treatments by the patient at home. Electronic monitoring has been shown to be the most accurate method of monitoring adherence compared with such other techniques as prescription refill records and self-reporting.[45] The 2009 Cystic Fibrosis Trust guidelines recommend that inhaler devices offer feedback on correct use and incorporate the ability to provide adherence data to clinicians.[46] The I-neb (available in the UK) incorporates Insight System software, which allows electronic monitoring of the number of times the device was used, the time of day, and the duration of each use. In a 1-year study of 28 children with CF, this technology demonstrated overall adherence to inhaled antibiotics of 60% to 70%, but with considerable variation within and between participants.[47] The I-neb Insight System also allows patients to upload their data from home onto a server, thus providing remote access of adherence data to their CF team. In this way, CF caregivers are able to work with patients to optimize their adherence and outcomes. This type of electronic data capture permits CF caregivers to interact with patients in an open partnership to achieve the common goals of improving drug delivery and reducing treatment burden. Adherence data can also be recorded with the AKITA SMART CARD, and technology exists to use wireless communication to transmit electronic adherence data. Although these monitoring technologies are not yet available worldwide and may impose more work on the health care team, the accurate measurement of adherence would allow the team to identify weaknesses and use strategies for improvement.

Behavioral strategies for improving adherence to treatment

Defining adherence

In order to support and encourage patients to maintain an often complex and time-consuming treatment regimen, clinicians must first understand how to approach the issue. Although many attempts have been made to define patient behavior when following treatment advice, the term most commonly used is adherence, which is described as an active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a desired preventive or therapeutic result.[48]

Acceptance of the disease, its implications, and the treatment required to maintain a state of health is key to how an individual copes with treatment requirements. Coping behaviors serve to prevent, avoid, or control emotional distress; consequently, in developing optimistic ways of coping, individuals believe that their own actions have an impact on their health, possibly leading to improved treatment adherence.[49]

Nonadherence can be interpreted as a method of controlling distress and blurring what is unacceptable, thereby providing a sanctuary from the realities of the disease. For a person growing up with CF, treatment demands become repetitive, often with no immediate perceived benefit.[50] Although most patients make every effort to live a "normal" life, deteriorating health often leads them to constantly redefine their version of normal.[51–53]

Evaluating nonadherence

Individuals with CF are required to carry out a multitude of often complex medical skills on a daily basis, which are both time-consuming and intrusive. Maintaining a treatment regimen is often an overwhelming responsibility, which can be made even more difficult when a child refuses to cooperate or a young adult has more interesting things to do.[8,54] Older children and adults report poor adherence to treatment regimens, describing them as wasteful of time, boring, and different from the normal lives of their peers. These young adults are determined to live as normal a life as possible and acknowledge that sometimes they are making an informed decision not to carry out their treatment.[55]

Many barriers to treatment adherence exist, mostly in the areas of personal health beliefs, coping styles, inadequate knowledge of the disease, peer group pressure, and family life. In addition, adherence has been shown to be influenced by gender, age, socioeconomic status, levels of functional impairment, poor adjustment, and stressful or traumatic events.[56] Other barriers more directly related to the health care setting include the behavior of, and interaction with, health care professionals, lack of information, the level of technically demanding skills, treatment burden, access to treatment, and length of time since diagnosis.[57] These barriers are understandable and, to a degree, reasonable. Health care professionals are often confused by the patient

who chooses not to adhere, however, making an informed decision not to follow a regimen with full understanding of the consequences, especially when evidence suggests that low rates of compliance are a predictor of disease exacerbation.[15] It is this knowing self-destruction that can be the most frustrating for health care professionals.

In a questionnaire-based survey, adolescents and adults with CF did not share their physician's perception of their disease severity, with consequent treatment adherence influenced by those perceptions. If patients thought they were well, regardless of the actual extent of their illness, they did not feel the need to follow treatment advice.[58] The impact of disease management on daily life creates both a practical and emotional interruption that may become lifelong. It is understandable that treatments are missed when there is no obvious or perceived benefit associated with them.

Measuring adherence

As stated earlier, nebulized treatments are often missed or overlooked because of the preparation and cleaning time involved, as well as the time needed for the actual nebulization process, which often includes more than one medication. Patients see this time as intruding into their daily lives, providing no immediate benefit, and becoming an obvious label of the disease.

Measuring adherence is an inexact science with many methods tried and failed, including patient reports, clinical assessment, checking dispensed prescriptions, bottle/tablet counts, blood tests, and urinalysis. Using electronic monitoring either covertly or overtly to assess adherence to nebulized therapy is probably the most accepted and the most valid.[47,49,59-62] Given that nebulized therapy is frequently missed, finding a reliable measurement is useful in planning an intervention and improving rates of adherence.

Strategies for modifying behavior

We find ourselves in a difficult position when a patient either refuses to adopt a treatment suggestion at the outset or is noncompliant with one or more treatments over time, and it is often at this stage that intervention is considered. A number of psychologically based therapies can be attempted when exploring reasons for nonadherence to treatment. Patients are individuals, however, and not all therapies will suit all patients. Thus, the clinical team and, most importantly, the clinical psychologist will assess each patient and try the most appropriate approach.

A collaborative approach to care

A collaborative approach to care is a partnership of equals and should take into account a patient's life experiences, personal health beliefs, and values, providing him or her with a shared responsibility with treatment planning and decision-making. In practicing a collaborative approach, clinicians will communicate with patients using flexibility and negotiation, as well as sharing facts and recommendations. In CF care, this approach will involve the patient as well as his or her family, usually the parents. Another term used in health care that embraces the collaborative approach is family- or patient-centered care. Collaborative care planning puts the family and the patient at the center of the consultation and encourages them to participate in treatment decision-making as a process.[63,64]

Motivational interviewing

Motivational interviewing (MI) uses a guiding style to engage with patients by establishing a conversation with them; however, it will only work with patients who are convinced about the need for change. The principles of MI include clarifying strengths and aspirations; expressing empathy; developing discrepancies among thoughts, beliefs, and behaviors; working with resistance to change rather than against it; evoking motivation for change; and promoting autonomy of decision-making. MI aims to help patients consider why and how they might change, with the therapist prompting, asking questions, summarizing, and clarifying whether change might be a possibility. Since it is the personal experience of the patient that is important in this type of therapeutic relationship, initially, the therapist must avoid offering his or her own perspective. When the patient is thought to be ready, however, the therapist can elicit practical solutions and offer suggestions.[65]

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a form of psychotherapy that focuses on changing certain thoughts, feelings, and behaviors, with the belief being that they are interconnected. Patients are encouraged to examine their thoughts and beliefs, and to understand the link to their behavior, moods, and physical reactions. CBT explores the underlying thoughts behind emotional problems, with the aim being to generate alternative, more balanced thoughts. Therapeutic sessions challenge negative, automatic assumptions with the intention of generating rational replies and realistic goals by introducing and building behavior modification. Homework is common with CBT, with patients asked to complete diaries or carry out tasks that will test assumptions that may be perpetuating the problem.[66,67]

Personal construct psychology

Personal construct psychology (PCP) assumes that we need to interpret reality according to our own models or personal constructs of how the world works. Problems arise when we do not change our personal constructs when they become harmful. PCP aims to help patients change their personal construct to a more viable option – for example, constructing an identity other than a person with CF. This means that the patient is being asked to try things out to see whether they work. This may not be a conscious or articulate construct, but may be inferred from behavioral changes. This form of therapy assumes that patients are experts in their illness; however, PCP acknowledges that illness perceptions and treatment cannot be separated from self-identity and self-esteem. PCP is often described as a way for individuals to manage their own problems, as patients know more about themselves than does anyone else. The purpose of PCP is to challenge negative perceptions and teach people to ask themselves questions about their own world views.[68]

Problem-solving therapy

Problem-solving therapy is a psychological intervention that aims to help individuals assess the negative impact of

problems, increase their ability to cope, and minimize the likelihood of similar problems reoccurring. This strategy is helpful for those who have poor problem-solving skills with an inability to generate alternative solutions, those who rely on others to solve their problems for them, and those who view all problems as unsolvable, and feel distressed and upset when faced with a problem.[69]

Conclusion

CF treatment regimens are lifelong, time-consuming, and differentiating, often with no immediate perceived benefit. It is no surprise, therefore, that persons with CF are nonadherent to aspects of their treatment regimen at different times throughout their lives. This behavior can be acknowledged as a normal adaptation to the physical and emotional intrusion of illness, in which avoidance can be a useful coping mechanism and form of control.[70]

Treatment with nebulized drugs has been shown to be one of the therapies with which patients are least likely to adhere; however, many potential therapies currently being investigated will be delivered by aerosol. Health care professionals need to work with patients and their families to dismantle the barriers to nonadherence and explore strategies, both behavioral and technical, that will assist in maintaining the treatment requirements of the future.

Conflict of interest statement

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Susan Madge, SRN, RSCN, MSc, MCGI, PhD – Advisory Committee/Board: Gilead Sciences, Inc.

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