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Orkambi™ For Cystic Fibrosis Before and After Lung Transplantation

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Orkambi™ (lumacaftor 200 mg/ivacaftor 125 mg) was approved in the U.S. in July 2015 to treat cystic fibrosis (CF) in patients 12 years and older in patients who are homozygous for the most common CF mutation delF508. This genotype accounts for approximately half of the CF population in the U.S. and a large percentage of patients worldwide. Because lumacaftor/ivacaftor has not been extensively tested in CF patients other than those homozygous for the delF508 mutation, patients must have a confirmed genotype prior to starting treatment.

In two double-blind, placebo-controlled studies, CF patients with FEV1 40-90% predicted who received lumacaftor/ivacaftor, two pills every 12 hours, demonstrated a 2.6-4.0% absolute improvement in % predicted FEV1 compared to those who took placebo over the 24 week study period. There was also a significant reduction in the rate of pulmonary exacerbations and a trend toward improvement in body mass index for those on drug. The most common side effects of lumacaftor/ivacaftor were shortness of breath, upper respiratory tract infection, nausea, diarrhea, and rash.

Although this drug approval is exciting and sets the stage for a new era in cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy, the effects of this drug combination appear to be modest. To put this in context, lumacaftor (Kalydeco™) which is approved for the treatment of CF patients with one or more copies of G551D or eight other gating mutations showed a much more robust clinical effect in its phase 3 study. Treatment with lumacaftor for CF patients with one or more copy of G551D was associated with a 10.5% absolute improvement in % predicted FEV1 compared to placebo (both at 24 and 48 weeks). In addition, lumacaftor was associated with significant improvements in all key secondary endpoints -including fewer pulmonary exacerbations, weight gain (nearly seven pounds on average), and reduction in sweat chloride.

Although lumacaftor/ivacaftor for delF508/delF508appears to have less clinical benefit compared to lumacaftor for gating mutations, there is certainly enthusiasm for its use in delF508 homozygotes given the severity of this genotype and the inherent complexity of correcting its defects. The bottom line is that modulator therapy is much more challenging in this group than in other CFTR mutation classes.

Although lumacaftor/ivacaftor was not tested in patients with advanced CF or after lung transplantation, the potential use of this drug combination is of great interest to the lung transplant

community. Patients, in particular, are likely to desire treatment with lumacaftor/ivacaftor given excitement over CFTR modulator therapy for this most common and most severe genotype. Despite the fact that the studies did not include patients with FEV1<40% predicted, it may be reasonable to extend treatment to advanced CF patients, even those awaiting lung transplantation, assuming there are no identified drug-drug interactions. Post transplantation, however, the use of lumacaftor/ivacaftor is fraught with issues due to its many drug-drug interactions with commonly used transplant medications.

The two components of Orkambi™ have different metabolism processes and drug/drug interaction profiles. Ivacaftor is a substrate of CYP3A which, when given as a single agent, is a weak inhibitor of CYP3A. The total adult daily dose of ivacaftor (Kalydeco™) is 300 mg.

Lumacaftor, on the other hand, is a strong inducer of CYP3A and results in "an internal drug-drug interaction" with ivacaftor and actually reduces ivacaftor levels. The fixed combination of Orkambi™ compensates for the strong inducer effect that lumacaftor has on ivacaftor with a total adult daily dose of 500 mg. The overall effect of the combination is a strong CYP3A induction. Lumacaftor has also been found to be an inducer and inhibitor of P-glycoprotein and in vitro has been found to be an inducer of CPY2B6, CYP2C8, CPY2C9, and CYP2C19.

The U.S. package insert of Orkambi™ advises against its use with CYP3A substrates (i.e. tacrolimus, sirolimus, and cyclosporine) with a narrow therapeutic index. In addition to a CNI or mTOR, most lung transplant recipients take a myriad of other medications with confounding interactions. Therefore, although tempting, combining lumacaftor/ivacaftor with a CNI or mTOR is likely to present considerable difficulties. To hit the highlights, the use of CYP3A inhibitors (such as azole anti-fungals) has no effect on lumacaftor, but significantly increases the exposure of ivacaftor. Lumacaftor/ivacaftor can reduce the exposure of and therefore the effectiveness of prednisone and methylprednisolone, therefore requiring higher doses of corticosteroids. Additionally, lumacaftor/ivacaftor can decrease the exposure and efficacy of proton pump inhibitors and H2 antagonists.

The list of concomitant medications investigated without drug interactions is short and includes among others, azithromycin, levofloxacin, ceftazidime, ciprofloxacin, and sulfamethoxazole/trimethoprim.

Without significantly changing standard immunosuppression and anti-infective regimens after transplant, lumacaftor/ivacaftor will be difficult to use after lung transplantation. One could argue that going to such trouble for a drug primarily focused on improving lung function and reducing CF pulmonary exacerbations is not worthwhile for patients whose CF lungs have already been replaced. In terms of its non-pulmonary effects, the modest improvement in BMI with lumacaftor/ivacaftor is not hugely compelling. While weight gain with this drug combination could reflect improved GI absorption due to normalized intestinal pH due to increased CFTR activity, it could also be a downstream effect of improved lung function and fewer pulmonary exacerbations. Thus, it is unclear if there would be any additional benefit of lumacaftor/ivacaftor given that this degree of weight gain occurs frequently in CF patients after lung transplantation. Other potential non-pulmonary benefits

such as improvement in sinus symptoms, less episodes of distal intestinal obstruction syndrome, etc. have not been well investigated.

In summary, the use of Orkambi™ after lung transplantation requires further study given its multiple drug-drug interactions and the fact that it may offer little benefit outside of its pulmonary effects. With that being said, combination therapy with lumacaftor/ivacaftor represents the first of its kind and changes the landscape for a large percentage of patients with CF. As drug development gets more precise and sophisticated, newer generation combination CFTR modulators are likely to follow. Despite its limitations and unclear role after lung transplantation, the prospect of targeted CTFR therapy holds great promise as a key strategy to preserve lung function over the decades and postpone the need for lung transplantation for these young patients.

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Challenges in Lung Transplantation for Anti-Synthetase Syndrome Associated Interstitial Lung Disease

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35-65% of patients with connective tissue diseases (CTD) such as scleroderma, rheumatoid arthritis, myositis, systemic lupus erythematosus and mixed connective tissue disease develop interstitial lung disease (ILD), depending on patient selection and detection methods [1]. According to the 2014 Report from the International Society for Heart and Lung Transplantation Registry, 1.4% of total transplants between January 1995 to June 2013 were done for CTD (586/41900) [2]. However, while grouped together under the "CTD-ILD" umbrella, each of these diseases presents unique challenges in the management of a potential lung transplant recipient [3]. Antisynthetase syndrome is one such distinct clinical phenotype comprised of inflammatory myopathy, ILD, Raynaud phenomenon, hyperkeratotic skin changes (mechanic's hands), and non-erosive arthritis in patients who have antibodies against aminoacyl transfer RNA synthetases [4]. The myositis in these patients ranges from being amyopathic to fulminant. Historically, many centers have been hesitant to perform lung transplants in this patient population due to existing comorbidities, risk of recurrence in the allograft, and poor long-term outcomes.

Patients with anti-synthetase syndrome may have sub-clinical cardiac involvement including myocarditis and conduction abnormalities that may be unmasked in the perioperative period [4]. In patients with end-stage lung disease, pulmonary hypertension is often a concomitant risk factor and may require the patient to be on cardiopulmonary bypass during transplantation, thus increasing the risk for primary graft dysfunction [1,5]. Some of these patients are malnourished, and may have muscle weakness due to their myositis superimposed on deconditioning, all of which can predispose them to hypoventilation [5]. Esophageal involvement in connective tissue diseases may also increase the risk for gastroesophageal reflux and thus the risk of developing chronic lung allograft dysfunction. Additionally, patients with antisynthetase syndrome are at an increased risk for malignancy, which one needs to be mindful of prior to listing for transplantation [3,5].

A major challenge in this population is refractory underlying disease. Many patients have progressed to end-stage lung disease despite being treated with prednisone, azathioprine or mycophenolate mofetil, cyclophosphamide, plasmapheresis and/or rituximab [1,6]. More recently, tacrolimus has also been used for steroid-refractory anti-synthetase syndrome [7]. Patients can develop diffuse alveolar hemorrhage or diffuse alveolar damage, and some of them have needed extracorporeal life support for refractory hypoxemia [8,9]. If the underlying disease cannot be adequately controlled prior to transplant, the successful prevention of recurrent disease in the allograft remains questionable. Unfortunately, there are no accurate markers of disease activity. A high creatine

phosphokinase or aldolase level certainly incites caution, but patients have had successful short-term and intermediate outcomes despite high levels [6].

Most of the outcomes of transplanting patients with anti-synthetase syndrome have been reported as case reports or a part of a larger cohort of patients who have been transplanted for CTD-ILD [9,10]. A 2012 report of 284 lung transplant recipients with CTD-ILD revealed that 5 year post-transplant survival for these patients was lower than that for COPD but comparable with IPF (73% versus 83% for COPD, 78% for IPF) [1]. More recently, data from the Leuven Transplant Cohort revealed that among 5 patients with pulmonary polymyositis (disease duration before lung transplant ranging from 2 months to 10 years), only 1 patient experienced acute rejection [6]. While the sample size was limited, none of these patients developed chronic rejection during follow-up (28-36 months). However, the length of hospital stay was longer in these patients compared to IPF and non-IPF non-IIM (idiopathic inflammatory myopathy) ILD cohorts. Both studies show that the increased complication risk appears to be mainly within the first 6-12 months after transplantation. Once beyond this period, the long-term outcomes are similar to the patients with other interstitial lung diseases.

Pulmonary and extrapulmonary recurrences of anti-synthetase syndrome are a major area of concern in this recipient population, complicating the recipient management and balance between augmenting immunosuppression and increasing the risk of infection. Recurrent diffuse alveolar hemorrhage and antibody-mediated allograft injury may delay extubation, increase the length of ICU, hospital or long-term acute care facility stay, or may even be fatal [1,8]. Worsening myopathy from myositis or intractable gastroesophageal reflux are also potential complications.

The abovementioned, limited reports suggest that lung transplantation may be successfully performed in patients with anti-synthetase syndrome. However, future research to identify accurate biomarkers is necessary to more clearly identify underlying disease activity. In the meanwhile, an organized, disease-specific multi-system evaluation must be performed in patients with antisynthetase syndrome who are being considered for lung transplantation.

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A Tale of Two Systems: Adult Lung Allograft Allocation Across the World

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First, two disclaimers: 1. There are probably almost as many nuanced versions of a lung allograft allocation system as there are countries (or cooperative groups of countries) performing lung transplantation; however, existing systems can generally be categorized according to whether or not they center on a net-benefit assessment. 2. While not exactly a tale of "the best of times" and "the worst of times," [1] the analogy holds true considering that we might be entering a new phase of streamlining and improving lung allograft allocation in a scientifically and ethically sound fashion.

Now that the disclaimers are out of the way, we can start with the United States model, which is perhaps the most scrutinized since the introduction of the Lung Allocation Score (LAS) in May 2005 [2]. The LAS replaced the previous model in which the length of time accrued on the waiting list was the primary determinant of allograft allocation with one based on "net transplant benefit," a measure based on waiting list and expected post-transplant survival probability. In doing so, the goal was to de-emphasize waiting list time and geography and emphasize transplant urgency (a measure of which is factored twice in the LAS) in order to reduce waiting list mortality and avoid inappropriate or futile transplants. Standardization was intended to increase allocation transparency and allow periodic data analysis to continually refine the LAS and its component variables [2,3], as occurred to great fanfare in February 2015 [4].

Although a full discussion of the impact of LAS is beyond the scope of this article, the consequences of the new system were a 54% reduction in the number of candidates on the waiting list [5] (as the perceived need to list patients pre-emptively to allow for time accrual was obviated) and a reduction in the median time on the waiting list from over 2 years to consistently under 200 days [5]. The LAS also contributed to a 3-fold increase in transplants in ICU patients who previously would not have accrued sufficient time on the waiting list. Similarly, allocation based on net benefit resulted in IPF surpassing COPD as the leading indication for transplantation5. Perhaps most significantly, the mortality on the waiting list decreased, fulfilling one of the main goals of the LAS, with absolute death counts declining from around 500 to under 300 a year and death rates per 1000 patient-years declining by 46% [5]. Although overall 1-year mortality remained stable post-LAS, reduced waiting list mortality came at the expense of increased perioperative morbidity and mortality among patients with high LAS [6].

The American experience led to consideration of the LAS for adoption more globally. Germany was the first country to adopt the LAS in December 2011, replacing a 3-tier system in which waiting list time determined order of transplant within each of the 3 tiers (highly urgent/ICU patients, urgent/hospitalized patients, and elective transplants) with the LAS [7]. A concurrent system of rescue allocation was adopted to allow the transplant of previously rejected organs into regional recipients regardless of LAS and accounted for about one third of procedures. Despite the potential dilutional effects of rescue allocation, the German LAS experience was fairly similar to the US experience with an increase in transplants for IPF and critically ill patients, a 23% reduction in waiting list mortality (although interestingly not for the IPF subgroup), and unchanged 3-month survival post-transplant [7].

Given the cooperation between Germany and 7 other European countries (Austria, Belgium, Croatia, Hungary, Luxembourg, the Netherlands, and Slovenia) as part of Eurotransplant [8], the German adoption of the LAS was somewhat of a gateway for the LAS in Europe: From December 2011, all countries within Eurotransplant agreed to enter LAS data on all highly urgent patients, arbitrarily defined as those with an LAS of 50 or above, for the international exchange of allograft offers. Subsequently, the Netherlands became the second country to officially adopt the LAS in April 2014. International allocation in Eurotransplant now proceeds as follows [8]: Patients with a high LAS from a country with a negative total balance with the donor country are positioned at the top of the donor country's match list, while those with a low LAS from a country with a negative total balance with the donor country are sorted among the donor country's patients according to LAS in the case of a German or Dutch donor or waitlist time in the case of non-LAS donors.

Despite differences in donor availability and competing national interests, international collaboration on organ exchange is a necessary reality of lung transplantation in smaller countries and has been shown to increase transplant activity and reduce waiting list mortality [9] within necessary constraints to minimize ischemic time. Such collaboration will likely pave the way for wider LAS adoption; this is most imminent in the Eurotransplant zone, where interest is growing in identifying factors predictive of mortality in all patient groups beyond waiting list time [10,11]. LAS and a modified LAS (called LASplus and including additional clinical factors such as ECMO, non-invasive ventilation, pneumothorax, and hemoptysis requiring bronchial artery embolization) have recently been validated as mortality predictors in Eurotransplant highly urgent and urgent patients, leading to the proposal of these net-benefit scores "as the basis for a new lung allocation policy in Eurotransplant" [11].

While other countries have not officially endorsed use of the LAS or similar net-benefit scores quite yet, there has been a trend of modifying waiting list policies to facilitate emergent transplants in patients who deteriorate and require mechanical ventilation or ECMO. So-called high-emergency allocation was instituted in France [12] and Switzerland [13] in July 2007 and more recently in Italy in November 2010 [14,15] with a significant increase in ICU transplants with lower, albeit acceptable mid-term survival. A similar trend has been seen in Canada, where some centers have added a third level of urgency to expedite transplantation of rapidly deteriorating patients whose urgency is not adequately defined by the existing 2-status classification of stable vs. deteriorating [16]. Scandiatransplant, the cooperative group regulating transplantation in Denmark, Finland, Iceland,

Norway, and Sweden, places patients on mechanical ventilation at the top of the shared waitlist [17,18].

The regulatory agency for transplantation in the United Kingdom, National Health Service Blood and Transplant, allocates allografts "based on need, benefit, and other clinical issues" within the zonal boundaries of each transplant center (similar to US organ procurement organizations), though the selection of recipients from local waiting lists is left to the discretion of transplant center physicians when an offer is available [19]. Australian allocation follows the UK model with physician discretion brought into play if more than one candidate meets size and blood type compatibility criteria. On the extreme end of the spectrum is Japan, where allocation continues to be done on a "first come, first served" basis [20].

In conclusion, while it may be overly simplistic to think of a net-benefit, LAS-based system as the panacea solving all the problems of pure waiting list time-based allocation, especially considering the historic limitations of the LAS in adequately prioritizing PAH patients [21], eliminating all disparities in access to transplant [22], or focusing on waiting list mortality at the expense of long term outcomes [6] and resource utilization [24], such a system is at least a promising start in standardizing allocation with a strong scientific basis that is adaptive to changes in patient characteristics and open to incorporating additional survival predictors as those become validated [3,25]. We are also starting to see more discussion about the role geography should or should not play in lung allocation and how to optimize that role in countries like the United States, where a national waiting list may not be practical, but broader geographical sharing is increasingly advocated [26,27]. As such, we may in fact be ushering in "the best of times," in which lung allocation is more transparent, ethical, and more importantly predicated on maximizing patient benefit, while minimizing patient harm, ultimately the goal of all our endeavors in medicine.

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Physician Training in Pulmonary Hypertension

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Pulmonary hypertension affects approximately 25 million individuals worldwide and causes premature disability and death from right ventricular (RV) failure. Specific pulmonary vasodilator medications are only indicated in patients with pulmonary arterial hypertension (PAH). Long-term mortality remains high despite considerable advances in medical therapy for PAH, largely as a result of right heart failure. There remains an unacceptable long delay from the onset of clinical symptoms to diagnosis, of approximately 2-3 years. Patients usually present when the pathologic changes are advanced and sometimes irreversible; many patients have already developed RV failure or are functional class III or IV. Diagnosis at this stage is associated with worse prognosis, emphasizing the importance of early disease diagnosis and aggressive treatment. Other, more common types of pulmonary hypertension, like pulmonary venous hypertension (from left-sided heart disease) or that one associated with hypoxia (from lung disease), do not benefit from specific pulmonary vasodilators and the treatment is focus on treating the underlying primary disease.

The management of pulmonary hypertension has advanced dramatically during the past 25 years but physician training lags behind. Expertise in the diagnosis and treatment of pulmonary hypertension remains scarce. Diagnosis and management of this disease requires a multidisciplinary approach and liberal referral to physicians experienced in evaluating and treating PAH, particularly to determine if patients will benefit from specific PAH vasodilator therapy. Delayed diagnosis and treatment of PAH are net effects of the gap between advancing knowledge and limited educational opportunity [1].

The American College of Graduate Medical Edition requires formal instruction, clinical experience, and demonstrated competence in evaluation and management of pulmonary hypertension [2,3]. Task force recommendations for competency in pulmonary medicine and cardiology include expectations for expertise in the assessment and management of pulmonary hypertension. However, the majority of pulmonary training programs in the United States offer little or no formal training in echocardiography, limited training in right-sided heart catheterization to evaluate pulmonary hypertension, and limited exposure to patients with PAH treated with advanced therapies, such as parental prostacyclins [1]. Cardiology fellowships routinely offer training in right-sided heart catheterization and echocardiography, but exposure to patients with the full spectrum of disease (eg, CTEPH, PAH, and life-saving therapies such as prostacyclins or pulmonary endarterectomy) are limited. Further, cardiology trainees perform right heart catheterizations during their "cath lab rotation" which is supervised mostly by interventional cardiologists. The majority of general cardiology fellows have limited exposure to advanced heart failure, pulmonary hypertension or congenital heart disease specialists, who performed their procedures with subspecialty fellows.

Individual cardiology or pulmonary trainees in the United States may use their elective rotations to gain additional training and experience related to pulmonary hypertension, but this additional training is left to the fellows' preferences and long term goals. Currently, there are a few opportunities for additional physician education and training directly related to pulmonary hypertension. The Pulmonary Hypertension Association funds fellowship awards for the development of investigators in this field. Specialized pulmonary vascular disease education is usually provided to cardiology fellows doing an additional year of training in the subspecialties of advanced heart failure and transplantation as well as adult congenital heart disease in some academic centers, but not all.

In order to improve outcomes in pulmonary hypertension, particularly in PAH, an earlier diagnosis is required to prevent irreversible RV changes and failure. Physician education is essential, particularly during cardiology and pulmonary fellowships as they are the 1st line specialists to evaluate patients with dyspnea and fatigue. We must teach trainees in both specialties- 1) the appropriate techniques during cardiac catheterization, particularly the importance of an accurate wedge pressure; 2) initial evaluation protocols / diagnostic tests needed; and 3) basic knowledge about side effects and mechanism of action in specialized PAH vasodilators, as not every patient will be able to be evaluated frequently at specialized centers and some request co-management.

The burden of pulmonary hypertension is likely to grow in the United States as patients age and develop chronic respiratory disorders and left ventricular diastolic dysfunction. The ever-present question of what patients will benefit or not of specific PAH vasodilators will be commonly discussed between cardiologists and pulmonologists. Appropriate fellowship education, with a minimum time of specialized training in pulmonary hypertension should be required for trainees, to achieve earlier pulmonary hypertension diagnosis and better evaluation and treatment of these patients.

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Update on Drug and Toxin Induced PAH – Truth and Fallacy

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Pulmonary arterial hypertension (PAH) is a rare and often fatal disease, commonly affecting middle-age women. It is commonly thought to be idiopathic or familial, or associated with important comorbid conditions including, but not limited to, connective tissue disease, portal hypertension, HIV, and congenital heart disease. An important and increasingly recognized cause of PAH includes exogenous exposures to drugs and toxins.

Historically, these toxins predominantly included anorexic drugs. Aminorex fumarate was a cause of PAH in parts of central Europe in the 1960s. Additional anorexic drugs were identified in the 1990s, specifically dexfenfluramine and fenfluramine (initially with a cluster of patients in France). It is sometimes argued that any prior use of these anorexigen drugs, regardless of duration of use or proximity to incident diagnosis of PAH, can be linked as causative in nature.

A case-control study published in 1996 blindly evaluated the use of anorexigen drug use in patients with PAH, and noted an increased odds ratio associated with recent use of dexfenfluramine or fenfluramine (10.1 if used within the year prior to index presentation). Importantly, any past use was associated with an odds ratio of 2.4, though this increased depending on the duration of use (1.8 if less than 3 months compared to a markedly increased 23.1 if used for more than 3 months).

In 2000, analysis of the Surveillance of North American Pulmonary Hypertension (SNAP) survey was performed specifically with an emphasis on exposures to anorexigens or other chemical substances. In this study, it was noted again that duration of use (greater than or equal to 6 months) and recent use (within 6 months) correlated with much higher odds ratios for the incident diagnosis of PAH.

The combination of the use of fenfluramine and phentermine ("Fen-Phen") became increasingly popular in the 1990s for weight loss, and gradually the number of cases of cardiac toxicity, including valvular and pulmonary vascular disease were increasing. Finally, in 1997, the FDA requested that the drug be withdrawn from the market. Thousands of lawsuits have been filed by patients treated with the drug, with billions of dollars designated for settlements. Even today, nearly 20 years after withdrawal from the market, ongoing lawsuits remain related to its use. The causative nature of its drug use with recent incident diagnoses of PAH, with a relatively prolonged latent period, remains controversial. There also appears to be a 'multi-hit' phenomenon that may incorporate remote use of these anorexigen drugs, in combination with additive associated risk factors, such as family history, HIV exposure, or the presence of connective tissue disease.

The mechanism by which anorexigen drugs cause PAH is not definitively known, though there remain multiple theories. These involve serotonin, which is a pulmonary vasoconstrictor, or via blockage of

potassium ion channels (IK) that leads to vasoconstriction. Pathologically, findings coincide with those found in idiopathic pulmonary arterial hypertension, including intimal and medial proliferation of myofibroblasts and plexiform lesions leading to pulmonary vascular scarring. Although a large proportion of those who were diagnosed with PAH related to aminorex or fenfluramine derivatives developed irreversible pulmonary arteriopathy, among survivors it has been noted that, in contrast to idiopathic or congenital heart disease-associated disease, the pulmonary vascular disease associated with anorexigen use can regress.

More recently, the category of "toxin" mediated pulmonary hypertension has expanded, as additional pharmacologic or recreational drugs have been implicated in the same pathologic and hemodynamic perturbations as described with previously withdrawn anorexigen drugs. Stimulants have been commonly described, with a predominant geographic cluster in the southwest United States, involving methamphetamine, amphetamine, and even cocaine use (this author has not yet viewed the drama series, 'Breaking Bad,' though anticipates an association between AMC network users and incident diagnoses of PAH since 2008).

In the world of hematologic malignancy, importantly, the use of tyrosine kinase inhibitors (TKI) have changed the natural history of chronic myelogenous leukemia (CML). Platelet derived growth factor (PDGF) is known to be involved in animal models of PH and human PAH. Particularly, imatinib, which blocks the PDGF receptor, has been studied favorably in its use as a potential treatment for PAH. Conversely, dasatinib is a TKI that inhibits a greater number of kinases, some with higher affinity, and although it is also used in the treatment of CML, it has been found to be associated with the diagnosis of PAH, often with a latent period between treatment and diagnosis of nearly three years. Discontinuation of drug is associated with clinical improvement and reversibility in some, but many patients require medical therapy for PAH.

Finally, interferons (IFNs) have been implicated recently in PAH, although additional studies are required to further demonstrate this. This group of proteins function as extracellular messengers related to immunomodulation, antiproliferation, and antiviral responses. The use of IFN-α has been implicated in PAH during or after its use for treatment of hepatitis C without portal hypertension, perhaps via thromboxane. In the treatment of multiple sclerosis, the use of IFN-β has been also associated with PAH.

In the current era of rapidly growing medical treatment options for PAH, the identification of drug and toxin associated disease is becoming increasingly important. Early recognition of exogenous exposure-associated PAH with appropriate reporting in the modern age, combined with aggressive and combination medical therapy often spanning across multiple pharmacologic classes, should favorably change the landscape and natural history of toxin and drug-associated PAH to one of reduced incidence and improved outcomes.

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Antibody Mediated Rejection

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Lung transplantation (LT) is a treatment option for patients with end-stage lung disease. Long-term survival, however, remains significantly worse in comparison to other solid organ transplants. Outcomes are limited by recurrent immunologic events contributing to chronic lung allograft dysfunction (CLAD), the very specifics of which remain unknown to this day.

Antibody-mediated rejection (AMR) is recognized as a form of rejection following kidney and heart transplantation with well-established diagnostic criteria regarding histopathology, immunopathology and serology, however, such strong evidence is somewhat lacking in regards to LT.

Some studies have identified the development of "de novo" Donor Specific Antibodies (DSA) as a significant predictor of poor outcomes. The presence of DSA is related to Bronchiolitis Obliterans (BO) and acute cellular rejection (ACR), specifically high grade and persistent-recurrent ACR (1-5). An In vitro study demonstrated that class I anti-HLA antibodies can induce airway epithelial cell proliferation, release of fibrogenic growth factors, and epithelial cell apoptosis. This process may lead to the activation of lung fibroblasts resulting in tissue remodeling and fibrous tissue proliferation observed during BO development [6].

The incidence of DSA remains unknown. Studies have described widely ranging results from 10 to more than 50% [7]. This inconsistency is largely due to significant differences in laboratory techniques and recipient variables, therefore definitive conclusions are difficult to draw. Moreover, tests are aimed to mainly identify HLA antibodies, neglecting other antigens that may have a pathogenic role in the humoral response such as collagen, vimentin, angiotensin-receptor and alpha-tubulin, minor histocompatibility antigens (MICA/MICB), as well as others that are yet to be defined.

Histopathologic and immunophenotypic criteria of AMR in LT have neither been described nor accepted. Unlike renal and cardiac transplant, they weren´t addressed in the 1990 and 1996 ISHLT classification of LT rejection and were not clearly established in the 2007 revision. The Pathology Council's update, provided in 2012 [8], described a broad list of patterns that would suggest AMR warranting immunopathologic evaluation. This list includes more specific terms such as neutrophilic capillaritis or neutrophilic septal margination, but also others like high-grade or persistent/recurrent cellular rejection, obliterative bronchiolitis and diffuse alveolar damage, which are found in processes like bacterial/viral infection, graft preservation injury and many others that are quite distant from AMR. In conclusion, there is no typical histopathologic pattern that would be considered specific for AMR, leaving clinicians without a reliable marker. The same is also true regarding exclusion criteria since presence of an absolutely healthy tissue is the only certain criterion for absence of AMR.

The bound antibody induces the complement cascade, leading to cleavage and activation of C4d protein. Thus, the presence of this complement protein in interstitial capillary is considered a marker of humoral damage of the allograft. This is used as a tenet in the AMR diagnosis algorithm, however many aspects of this phenomena remain unknown. Furthermore, the complement cascade can be activated by bacterial infection and other inflammatory processes, rendering this marker somewhat unspecific. There are few published schemes for grading distribution or intensity of C4d staining in pulmonary AMR. Usually immunoreactivity higher than 50% of interstitial capillaries is used as a threshold; however, as mentioned previously, there is a big gap of knowledge owing to scarcity of studies and heterogeneity in methods and results amongst them. We are still far away from fully understanding the true role of staining complement proteins and the best way to measure them.

Banff criteria defined AMR as an unexplained graft dysfunction, "de novo" DSA, neutrophilic capillaritis and positive C4d staining in biopsy [9]. Unlike renal or cardiac transplant, it is very uncommon to find patients who fulfill all the criteria. As discussed above, AMR is presented by a large spectrum of histopathologic patterns that are established in nearly all lung biopsy samples and normal tissue is the only true evidence for exclusion of AMR. C4d is still far from being sensitive or specific enough to be considered as an irrefutable marker. DSA presence should be considered as a mainstay of this process, however they may be adsorbed within the allograft, leading to falsely negative results [10]. As in cellular rejection, patients may develop acute respiratory symptoms or remain totally asymptomatic with normal pulmonary function tests. Therefore we still need to define a diagnostic algorithm for AMR that fits this lung idiosyncrasy.

Response to treatment and long-term outcomes are two important areas needing further investigation. Few small trials have been published with unclear and heterogeneous results. Therapies are based on combinations of plasmapheresis, intravenous immunoglobulins, high dose glucocorticoids and Rituximab. Some centers used Bortezomib or Eculizumab in complex cases.

In conclusion, there are numerous vitally important knowledge gaps in AMR, LT failure, and management. First, we need to develop a concrete definition and diagnostic criteria for AMR. Only then we could perform large multicenter and well-designed trials to evaluate therapies as well as short and long-term outcomes.

In this author's opinion, we are only beginning to realize the magnitude of this medical complication, whether it´s just an isolated condition, only important to a small cohort of patients, or the presence of a humoral response determines immunologic/inflammatory processes that may contribute to the development of CLAD. It is prudent to ask new questions, seek answers to them, and investigate those answers in the hopes of progressing the very science and medicine of lung transplantation and improving our patient's long-term outcomes.

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THE ASPEN LUNG CONFERENCE 2016: "Lung Transplantation: Opportunities for Repair and Regeneration" June 8-11, 2016 @ The Gant Conference Center, Aspen, Colorado

Dear ISHLT membership:

We are pleased to announce that the 59th Thomas L. Petty Aspen Lung Conference will be devoted to lung transplantation! The Aspen Lung Conference is one of the most respected and innovative meetings in the North American lung research community at large: With a focus on clinical problems affecting the lung, the Aspen Lung Conference blends cutting-edge basic and clinical research in a setting that facilitates extensive discussion amongst participants. This is the very first time that lung transplantation will be the topic of discussion. The conference will be organized around a central theme of the life cycle of a lung transplant, spanning donation, explantation, preservation, implantation and finally accommodation. Emphasis will be placed on integration of basic, translational and clinical sciences. The program will be organized into a series of thematic sessions focusing on (i) new concepts in lung allograft preservation and reconditioning utilizing ex-vivo lung perfusion, (ii) adaptive immunity including new arenas in T cell and B cell biology, (iii) host response/innate immune mechanisms, (iv) airway/allograft remodeling and (v) strategic approaches to translating scientific advances into meaningful therapies including molecular phenotyping, novel immunosuppression and development of novel diagnostic and monitoring techniques. The overall objective is to assemble thought leaders and learners of transplantation to educate the next generation of scientists and define the next big steps to be taken in the field. We hope many of you will consider submitting an abstract (which can overlap your ISHLT, AST, or ATS submissions). **Abstract deadline is February 14, 2016**. For more information, contact: Jeanne Cleary, E-Mail: Jeanne.Cleary@ucdenver.edu or visit our website at www.aspenlungconference.org. We hope to see you in Aspen!

Martin Zamora (Chair)
Mark Nicolls & Tereza Martinu (Co-Chairs)

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EDITOR'S CORNER: From the Man of Action to the Veto President

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Hiram Ulysses Grant was erroneously listed as Ulysses Simpson Grant when recommended for the U.S. Military Academy at West Point. This son of a leather tanner was born in Point Pleasant, Ohio on April 27, 1822. Following graduation from West Point in 1843, he started his military career and fought in the Mexican War then resigned in 1854. He later accepted command of a company of Illinois volunteers in 1861 just after the outset of the Civil War. Within a year, he rose to brigadier general and achieved national fame for his efforts at the Battle of Fort Donelson in Tennessee. He was nicknamed "Unconditional Surrender" which matched his "U.S." initials because he refused any terms other than "unconditional and immediate surrender" from Confederate forces. Although Grant suffered heavy losses at the Battle of Shiloh in Tennessee in April 1862, he became a national hero for his bravery in key victories at Vicksburg, Mississippi in July 1863 and at the Battle of Chattanooga, Tennessee in November 1863. Following which Grant was appointed General-in-Chief of the U.S. Army by President Abraham Lincoln in 1864. On April 9, 1865, he accepted the Confederate surrender by General Robert E. Lee at the Appomattox Courthouse in Virginia thus ending the Civil War and earning him the nickname, "**Hero of Appomattox**." Because of personal popularity, he easily won the election of 1868 and became the 18th President. This Great War hero proved to be a poor chief executive primarily by putting friends in high positions. He was scrupulously honest and popular, but his administration was marred by the dishonesty of those he trusted.

Grant was never able to end the corruption that undermined his presidency. By the end of eight years, every single one of his executive offices had come under congressional investigation. He stated, "*I never wanted to get out of a place as much as I did to get out of the presidency*." But after he left office, his bad luck continued. He continued to trust others more than he should and he became the victim of an incredible Wall Street fraud that left him bankrupt. Desperate to provide for his wife and children, Grant took advice from his friend, Mark Twain, and began writing his memoirs as a source of income. He had barely begun work when a final crisis threatened during the summer of 1884. He was eating a piece of fruit, grabbed his throat and exclaimed, "*I think something has stung me from that peach!*" Grant's cigar habits had caught up with him, he had developed throat cancer. By the following summer, working hard to complete his memoirs at a cottage in the Adirondacks, Grant knew his end was near. "*There cannot be a hope of going far beyond this time*," he confessed, "*it is nearly impossible for me to swallow. It pains me even to talk*." Writing in extreme pain, he produced a brilliant autobiography of lasting literary value and he forced himself to stay alive until he completed it. Perhaps not surprisingly, Grant chose to write almost nothing at all about the loneliness and misery of his early life and he commented only briefly on events of his presidency. Instead, he wrote about the only time in his life he had truly succeeded, in war. He died of throat cancer on July 23, 1885 in Mount McGregor, New York emaciated down to 100 pounds. He left us

with these words, "***Although a soldier by profession, I have never felt any sort of fondness for war, and I have never advocated it, except as a means of peace."*** The major events of his presidency included: the completion of the transcontinental railroad, the establishment of Yellowstone, the first national park, and the invention of Alexander Graham Bell's telephone.

A graduate of Harvard Law School in 1845, **Rutherford Birchard Hayes** of Delaware, Ohio was born on October 4, 1922. At the start of the Civil War, he became a major in the 23rd Ohio Volunteer Infantry and rose to the rank of brevet major general. He was wounded during the Battle of South Mountain in Maryland in 1862 and took part in the second Battle of Winchester and the Battle of Cedar Creek in Virginia in 1864. He won a seat in the U.S. House of Representatives but did not take this position until after the Union victory in April 1865. He was a popular figure and a war hero in Ohio where he served three terms as Governor. He became the 19th President of the United States in one of the most contentious elections in history. Samuel J Tilden of New York won the 1876 popular vote, but neither candidate won enough Electoral College votes, Tilden, 184 and Hayes, 165. Twenty Electoral votes were disputed from South Carolina, Louisiana and Florida. The electoral commission awarded Hayes all 20 and because of the political division surrounding the election, he secretly took the oath of office in the White House two days before his inauguration on March 5, 1877. Hayes was not a familiar leader outside the state of Ohio, for this he was nicknamed, **"The Great Unknown."** He did bring in badly needed integrity, skill and a measure of stability into a war-torn nation. President Hayes revolutionized the system of government appointments based on merit and not by political or personal ties (the spoils system). He fought for the rights of minorities and the poor, especially in the South and ended Reconstruction by withdrawing Federal troops from the south and appointing former Confederates to government positions. His economic policies engendered confidence among business leaders. Among the technological advancements during his time were Thomas Edison's phonograph and incandescent lamp along with the installation of the first telephone in the White House by Alexander Graham Bell. He refused to seek a second term as promised and turned over a prosperous and peaceful nation to his successor. His memorable quote, "***he serves his party best who serves his country best***." He retired and died in Fremont, Ohio on January 17, 1893 of a heart attack "neuralgia of the heart."

James Abram Garfield, the last of a series of "Log Cabin" Presidents from poverty, was born on November 19, 1831 in Cuyahoga County, Ohio. Raised by his widowed mother from the age of 2, he worked on odd jobs and canal boats to put himself through Williams College in Massachusetts. He graduated in 1856 and became a classics professor and college president at Western Reserve Eclectic Institute (later Hiram College in 1857). He won a seat in the Ohio Senate and became a member of the new Republican Party with his fierce and vociferous opposition to slavery. He joined the Ohio Volunteer Infantry after the start of the Civil War. He commanded a brigade at the battle of Shiloh in 1862 and participated in the battle of Chickamauga in 1863. He was a major general when he reluctantly resigned from the army as persuaded by President Abraham Lincoln to take a seat in the U.S. House of Representatives in late 1863. Lincoln found Garfield more valuable as a loyal Republican in Congress than on the battlefield. He was re-elected to the house for eight consecutive terms and became the only sitting member in the House to be elected President. As the 20th President, he was renowned scholar and professor, we was known as the "**Teacher President**." His stance against political corruption cost him his life. He was shot on July 2, 1881 in Washington, DC

by a disgruntled office seeker, Attorney Charles Julius Guiteau. Mortally wounded, he was bedridden and essentially incapacitated until his death some 79 days later when he died on the New Jersey shore at Elberon on September 19, 1881 from an infection caused by the bullet wound. He was the second President killed by an assassin's bullet (Lincoln, the first) and his 199 days in office was the second-shortest after Wiliam H. Harrison's 32 days. Other than the founding of the American Red Cross, there were no meaningful decisions or legislation during his brief Presidency. We are graced by these words he left us, "***Next in importance to freedom and justice is popular education, without which neither freedom nor justice can be permanently maintained."***

"**Elegant Arthur**," was born in Fairfield, Vermont on October 5, 1829. He was a teacher, studied law, admitted to the bar and practice law in New York City. Although he saw no military action, he achieved rank of brigadier general for providing supplies to the troops. He was against slavery, supported Abraham Lincoln and Ulysses S Grant. President Grant appointed **Chester Alan Arthur** as collector of the Port of New York out of loyalty. This position at the nation's busiest port was lucrative, powerful and responsible for operating the customs house and hiring thousands. Before his presidency, Arthur was a benefactor and promoter of the spoils system within government service as such one was hired and promoted based on political allegiance and not necessarily on competence. In 1878 Hayes removed Arthur from his position as part of his reform of the Port of New York and crusade to end the spoils system. As the 21st President many worried about his close association with supporters of the spoils system. However, President Arthur confounded his critics by passage of the Pendleton Government Jobs Act which reformed civil service, accomplished Hayes' crusade and eliminated the spoils system. In 1881, he was the third President to hold office within a year which has only occurred once in US history. Hayes' term ended March 4, Garfield was assassinated and Vice President Arthur became President on September 20, 1881. Arthur was renowned for his stylish appearance. Tall and distinguished, many believed he looked like a President. His most visible public appearance occurred on February 21, 1885 during the dedication of the Washington Monument in Washington, DC. He contracted Bright's Disease or chronic glomerulonephritis soon after taking office, suffered in secrecy during his Presidency and died of cerebral hemorrhage on November 18, 1886 in New York City. His memorable quote was "***Men may die, but the fabrics of our free institutions remain unshaken."***

Stephen Grover Cleveland was born in Caldwell, New Jersey on March 18, 1837. Unable to afford college, he studied law on his own in Buffalo. He was admitted to the New York bar and became renowned for his honesty and intelligence. Cleveland was elected sheriff in Erie County where he carried out executions by personally hanging convicted criminals. He was elected mayor of Buffalo and developed a reputation as a law-abiding reformer who was trustworthy and fought corruption. Within a year, he was elected Governor of New York. Within two years, he was elected the 22nd President of the United States and the first Democrat to be elected President after the Civil War. His most distinctive physical features were his drooping moustache and bow tie. Cleveland was a bachelor when inaugurated in 1885 and was the only President married in the White House to 21-year-old Frances Folsom at a White House ceremony on June 2, 1886. She remains the youngest First Lady in history. During his presidency, he fought corruption with a policy to appoint people to government based on merit and not on political cronyism. He vetoed many bills most of which were fraudulent Civil War pensions. He coerced the railroad system to return millions of acres of western

lands provided by the government that were not used for its intended purposes. Because of the number of bills he vetoed he was nicknamed "**Veto President**." His most famous appearance occurred at the dedication of the Statue of Liberty in New York Harbor on October 28, 1886. He will later be elected the 24th President, but for this presidency we are left with this memorable quote, "**A truly American sentiment recognizes the dignity of labor and that fact that honor lies in honest toil**." Two final points, his biographer, Allan Nevins attests, "*It is as a … man of character that Cleveland will live in history*." Also, when the Clevelands left the White House after his first term in 1889, the First Lady told the servants, "*I want to find everything just as it is when we come back again…*" She was right, they moved in again in 1893.

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EDITOR'S CORNER: Selected Key Figures who Shaped 19th Century America

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John Marshall was a veteran of the Revolutionary War, a congressman and Secretary of State. Above all, he was the "**Great Chief Justice**." From 1801-1835, his vision and leadership established the Supreme Court as the defender of the Constitution. Marshall was appointed Chief Justice by President John Adams. Up to that time, the Court had been a weak collection of political appointees. Each judge issued an individual opinion on cases brought before him. Determined to forge a strong Court, Marshall established a new policy called "*the opinion of the Court*." Under this policy, a forceful majority ruling was issued in each case. One of the Marshall Court's most important rulings dealt with the 1803 case *Marbury vs Madison*. Marshall ruled that the constitution was the highest law of the land, and that the Supreme Court could strike down any law made by Congress that violated the Constitution. This concept, called "*judicial review*," became a central feature of the American system of government. Unlike Thomas Jefferson, John Marshall did not believe in a strict interpretation of the words of the Constitution. He believed that its underlying ideas should be "*adapted to various crises of human affairs*."

John C Calhoun held many high government posts in the years before the Civil War. He represented South Carolina in both the House of Representatives and the Senate. He was President James Monroe's Secretary of War and President John Tyler's Secretary of State. He was Vice President under Presidents John Quincy Adams and Andrew Jackson. But he is best remembered as the South's leading spokesman for slavery, which he regarded as "*a positive good*," and for the right of states to override national law. When Calhoun first entered Congress in 1811, he joined the "War Hawks," a group that helped bring about the War of 1812 with Britain. At that time, Calhoun supported a strong government. But later he changed his mind and began arguing that states did not have to obey federal laws they considered unconstitutional. He believed that states could cancel, or "nullify" laws they disliked. His final, most vigorous fight was against the Compromise of 1850, which admitted California as a free state and outlawed the slave trade in the District of Columbia. Just before his death on March 31, 1850, Calhoun sighed, "The South, the poor South! God knows what will become of her."

Take note, in 1832, Calhoun resigned as Vice President to take a Senate seat. The only other Vice President to resign was Spiro Agnew, who left office in 1973 over charges of tax evasion.

Daniel Webster, a brilliant orator and a passionate defender of the federal government delivered these famous words in 1830, "*Liberty and Union, now and forever, one and inseparable*." A graduate of Dartmouth, Webster won fame as a lawyer. In several cases argued before the Supreme Court, Webster spoke in favor of a strong national government and a free interpretation of the Constitution.

Elected to Congress in 1813 from New Hampshire, and later from Massachusetts, he became a leader of the Whig Party and one of the most influential figures in Washington. He forcefully argued against the Southern belief that states had the right to nullify federal laws they did not agree with. Although he despised slavery, he supported compromises that he hoped would keep the Union together and avert civil war. Twice, he served as Secretary of State. In that office, he helped put a stop to the African slave trade. Daniel Webster never achieved his goal to be President. But his contributions to the nation was enormous. "*You have manifested powers of intellect of the highest order and in all things, a true American heart*." President John Tyler said to Webster. In 1957, a Senate committee headed by John F Kennedy chose Webster as one of the five outstanding senators of the past.

Henry Clay was a slave owner, but he urged the elimination of slavery. In the turbulent years before the Civil War, when the issue of slavery threatened to split the U.S. apart, Henry Clay did more than any other leader to keep the country together. For his efforts to save the Union, Clay became known as the "**the Great Compromiser**." During his long career, Clay served as a congressman and senator from Kentucky, as Speaker of the House, and as Secretary of State. He ran for the presidency three times but was never elected. Told once that a speech he had given had hurt his chances for presidency, he replied, "*I would rather be right than president*." As a young congressman, Clay developed an economic program called the American System, which called for federally financed roads and canals, a national bank, and high tariffs. Later, when slavery threatened to divide the country, he worked for solutions that North and South could accept. In 1829, he helped pass the Missouri Compromise. It kept the number of slave and free states equal, admitting Maine as a free state and Missouri as a slave state. In 1832, when South Carolina threatened to secede over a tariff dispute, Clay devised a compromise that ended the crisis. And in 1850, when California asked to enter as a free state, Clay drew up the Compromise of 1850, a group of bills with provisions that both North and South wanted. But Clay's compromise kept the Union together for only 10 more years.

Sojourner Truth was an illiterate and tall African-American woman who when she spoke out against slavery, she held everyone spellbound. She would begin every speech..."*Children, I talk to God and God talks to me*." Born a slave named Isabella on a farm in New York, she earned her freedom around age 30 after New York abolished slavery. She believed God had wanted her to "*travel up and down the land*" to preach his word. Therefore, she took the name Sojourner (which means wanderer) Truth and spoke wherever there was an audience. Her eloquence made her so famous that in 1864 President Lincoln invited her to the White House and appointed her counselor to freedmen in the capital. Following the Civil War she helped newly free slaves and improved the lives of women.

William H. Seward was a lawyer from upstate New York who served as governor of New York and was elected to the U.S. Senate. He was a staunch opponent of slavery. He lost the Republican nomination for President in 1860 to Abraham Lincoln. He would later support Lincoln and thus was rewarded the post of Secretary of State under Lincoln's administration. During the Civil War, Seward carefully negotiated and dissuaded France and England from supporting the South. When Lincoln was assassinated, Seward was shot by a co-conspirator. He recovered and remained in his position under Andrew Johnson. With Johnson's support he purchased Alaska from Russia for $7.2 million, roughly two cents an acre. His critics called this purchase "Seward's Folly, however he predicted that

this vast northern area would bring great wealth. Decades later, with the discovery of gold, oil and natural gas in Alaska he was proven correct.

The bright and eager **Dorothea Dix** established a girls' school in Boston at the age of 14. She taught for 14 years but gave it up after several bouts of tuberculosis. She visited a Cambridge jail in 1841 to teach Sunday School and instead became horrified to find mentally ill patients imprisoned like criminals. She then began a lifetime of service for those who could not speak for themselves. During her tours of other Massachusetts jails and poorhouses she found the mentally ill chained, beaten and locked unclothed in closets or cellars. IN 1843 she began a campaign to establish separate hospitals for the mentally ill where they could be humanely treated. Because of her efforts, the care and facilities for the mentally ill improved not only in the U.S. but also in Canada and England. She did serve as superintendent of women nurse in the Union army.

The idea of woman doctor was shocking in the 1840's. However, **Elizabeth Blackwell** from England moved with her family to the United States when she was 11 in 1832. She was determined to practice medicine and succeeded against all odds. She grew up in Cincinnati, Ohio and started teaching school to support her family after her father died. She applied to and was rejected by 29 medical schools. In 1847, she was accepted by Geneva Medical College in western New York. She graduated two years later and after further study in Europe, moved to New York City to begin medical practice. She found closed doors everywhere she went and no hospital accepted a woman doctor. In 1857 she founded the New York Infirmary for Women and Children, a hospital run almost entirely by women including her sister Emily who also was a doctor. She founded the Women's Medical College in New York and the London School of Medicine for Women in England.

The "***Moses of her people***," **Harriet Tubman** led enslaved people to freedom. She was born into slavery on a Maryland plantation where two of her sisters were sold and she, brutally beaten. In 1849, she escaped and headed for the city of brotherly love, Philadelphia. She dedicated her life to helping other African-Americans escape from bondage. Tubman became the most famous "conductors" on the Underground Railroad, a secret network of safe houses providing refuge for escaped slaves. She made many dangerous trips to the South and helped more than 300 slaves to freedom in the North. Tubman hid during the day and led slaves to freedom by night guided by the North Star. Angry slaveholders offered a $40,000 reward for her capture, but she was never caught. She served as a cook, nurse, scout and spy for the Union army during the Civil War. After the war, she continued to work for her people, raised money, set up schools and established homes for former slaves and their families. At her death in 1913, she was buried with full military honors.

Clara Barton was the "angel of the battlefield." She helped wounded and dying soldiers during the Civil War which made her a national heroine. A strong-minded woman, she devoted her life to helping others. At the outset of the Civil War in 1861, Barton was the first female clerk to work in the Patent Office in Washington, D.C. Reports of suffering soldiers motivated her to action. She nursed the wounded and carried supplies and medicines to the battlefield. Her war efforts exhausted and sickened her. In 1869, she went to Switzerland to recover. While in Switzerland, she learned about the International Red Cross, an organization devoted to the relief of suffering resulting from war. She took part in Red Cross activities during the Franco-Prussian War in 1870-1871. In 1873, she

returned home and created the American Red Cross. She served as the organization's first president for 22 years and expanded the Red Cross to include helping victims of peacetime disasters, including floods and hurricanes.

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