出國報告(出國類別：參加國際會議)

2010 年美國胸腔學會國際年會

服務機關：國防醫學院三軍總醫院
姓名職稱：張 宏、主治醫師
派赴國家：美國
報告日期：99 年 6 月 1 日
出國時間：99 年 5 月 13 日至 5 月 21 日

一、 摘要：

參加美國胸腔學會國際會議主要的目的是展示“以螢光微粒技術及胸部電腦斷層探討急性肺損傷後局部肺血流及肺容積分佈變化”，藉此機會與世界頂尖及相關領域的學者專家交流並接受指正且尋求研究議題。並且參加研究課程且吸收新知及世界潮流的動向。期望對於肺癌、慢性阻塞性肺部疾病及肺容積縮減手術有進一步的認識及瞭解。

投稿摘要如下

目的:有效率的氣體交換端視局部肺血流及通氣的分佈完全吻合，過去的研究顯示肺局部血流及通氣的分佈受到重力、肺容積變化及缺氧性肺血管收縮等因素影響。最近的研究用高解析度螢光顆粒球標記局部肺血流及通氣，發現肺血管及支氣管的分叉構造才是主要決定肺血流及通氣的因素。這新發現對於肺血流分佈過去的認知提出嚴重的質疑。我們假設移植肺與存留肺局部肺血流分佈不同並且局部通氣及血流吻合於存留肺較移植肺有效率。

方法: 用八隻豬分別在左側側躺以及右側側躺兩種不同的姿勢,在不同的姿勢分別注入不同顏色 1-μm 和 15-μm 的螢光微粒。在實驗結束後取肺並用壓力 25 cm H_20 的空氣吹乾。吹乾之後將肺用發泡劑封肺,並切成每塊 1.7cm^3的肺塊去讀取其螢光值。在分析其V/Q比值。

結果: 正躺與RLD比較 PO_2 增加 (175±23 vs. 236±14) mmHg, and $P(A-a)O_2$ 減少 (45±8 vs. 12±6) mmHg . 區域的肺部血流不論是左或右肺均是自上而下增加；在 LLD & RLD 姿勢之下，dependent lung 的肺血流會比 non-dependent lung 有較高的垂直差異 (vertical gradient)；而明顯的等重力血流之異質性(isogravitational blood flow heterogeneity) 則可見於 LLD & RLD姿勢之下。 10 cm H_2O的PEEP則可讓不論是左或右肺的區域血流更平均與同質化。

結論: 顯示肺部撐開通氣對於肺損傷及塌陷的肺有保護及立即改善的作用且肺分流及肺死腔亦會減少。局部肺血流及通氣順著重力的方向增加，此時背部明顯大於腹側，氣體交換及通氣血流的吻合逐漸恢復正常並有大幅度的改善。

參加 2010 年美國胸腔國際會議出國報告目錄

二、 本文：

1. **目的：** 參加美國胸腔學會國際會議主要的目的是展示“以螢光微粒技術及胸部電腦斷層探討急性肺損傷後局部肺血流及肺容積分佈變化”，藉此機會與世界頂尖及相關領域的學者專家交流並接受指正且尋求研究議題。並且參加研究課程且吸收新知及世界潮流的動向。期望對於肺癌、慢性阻塞性肺部疾病及肺容積縮減手術有進一步的認識及瞭解。

2. **過程：** 2010 年 5 月 13 日飛去美國新奧爾良完成報到手續參加美國胸腔學會國際會議。

99 年	5 月	13 日	大會報到
99 年	5 月	14 日	ATS Meet the Professor Seminars
99 年	5 月	15 日	ATS Meet the Professor Seminars
99 年	5 月	16 日	參加 BENCH TO BEDSIDE: THE ART AND SCIENCE OF TRANSLATIONAL RESEARCH 課程
99 年	5 月	17 日	張貼 poster
99 年	5 月	18 日	參加 THE TRANSLATIONAL BIOLOGY OF LUNG CANCER 課程
99 年	5 月	19 日	大會結束

3. **心得：**

- 有關肺癌的篩檢及肺結節的處理 Dr. Van Klaveren 以胸部電腦斷層於 NELSON trial 中，以 7557 個病人於第 1、2、4 年篩檢，結節體積大於 25%即認定結節長大及生長過速，篩檢的敏感度高達 94.6%，negative predict value 是 99.9%。第一次檢查是陰性後 1 及 2 年檢查發現肺癌的機率分別是 1/1000 及 3/1000。Quantitative imaging 將是評估肺結節的重要工具。此篇結果發表於 N Engl Med 2009；361：2221-2229。
- 有關 mutation in lung cancer，Dr. Shaw AT 發表於 J clin Oncol 2009；27：

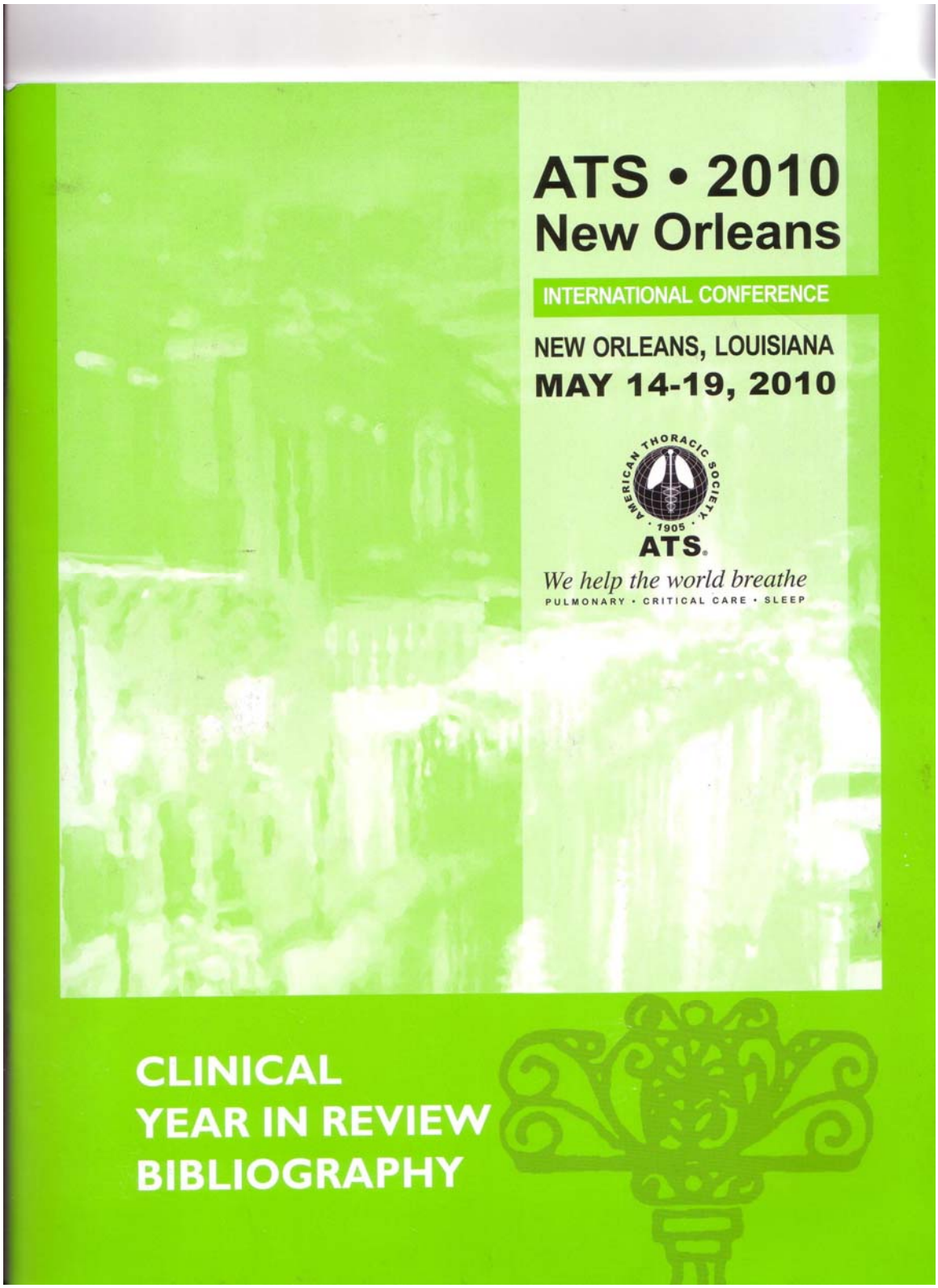
4247-4253 討論非小細胞腺癌含 EML4-ALK fusion tumor 大多是年輕人，男性，不抽菸，肺腺癌，並對 EGFR TKIs 有抗藥性。EML4-ALK 可以 Fluorescent in situ hybridization 及 immuno-histochemistry stain 來認定。病人若顯示此基因並以 EGFR TKIs 治療無效需考慮 ALK targeted agents

- 有關 molecular therapeutic in lung caner Dr. Mokts 等發表 Gefitinib 或 Carboplatin-paclitaxel in pulmonary adenocarcinoma 於 N Engl Med 2009；361：947-957 提及 609 個肺腺癌病患，不吸菸隨機抽樣分組接受 gefitinib (250mg per day) 或 carboplatin 及 paclitaxel 治療。12-month rates of progression-free survival 服用 gefitinib 是 24.9% 接受 carboplatin -paclitaxel 是 6.7%。 俱有 EGFR mutation 以 gefitinib 治療較有效，若不具 EGFR mutation 以 carboplatin-paclitaxel 治療較有效。2.6% 人會產生 interstitial lung disease 0.5%造成死亡。EGFR mutation 較常發現於女性，不吸煙及肺腺癌患者。
- Dr. Bass AJ 發表於 Nat Genetics 2009；41：1238-1242 提到 sox2 是 amplified lineage-survival oncogene 於肺及食道鱗狀上皮細胞癌，於肺上皮細胞癌發現 genomic amplification on chromosome 3g26.33 含 transcription factor gene sox2。此基因可以促進 basal tracheal cells 分化及增生及引發 pluripotent stem cells。另外 ectopic expression of sox2 常和 foxE1 或 EGFR2 合作 transform immortalized tracheobronchial 上皮細胞。Dr. Kevin R. Flaherty review 肺間質疾病引用 Dr. Fell co 發表於 Am J Respir Crit Care Med. 2010 181181：832-7 討論 clinical predictors of a diagnosis of idiopathic pulmonary fibrosis 回溯分析密西根大學附設醫院 664 位 idiopathic pulmonary fibrosis 病患發現 increase age 及 total HRCT interstitial score 可以預測 IPF 的存在。肺功能、性別、six minute walk test de-saturation 或 distance walked 無法預測 IPF。

4. 建議：

1、由於研究實驗需投入心血耗時損力，希望能全額補助參展者以鼓勵良好基礎及臨床醫學之研發。
2、對於特定課程 (Postgraduate Course)新知教授亦能給予補助。

參. 附錄：參加會議之資料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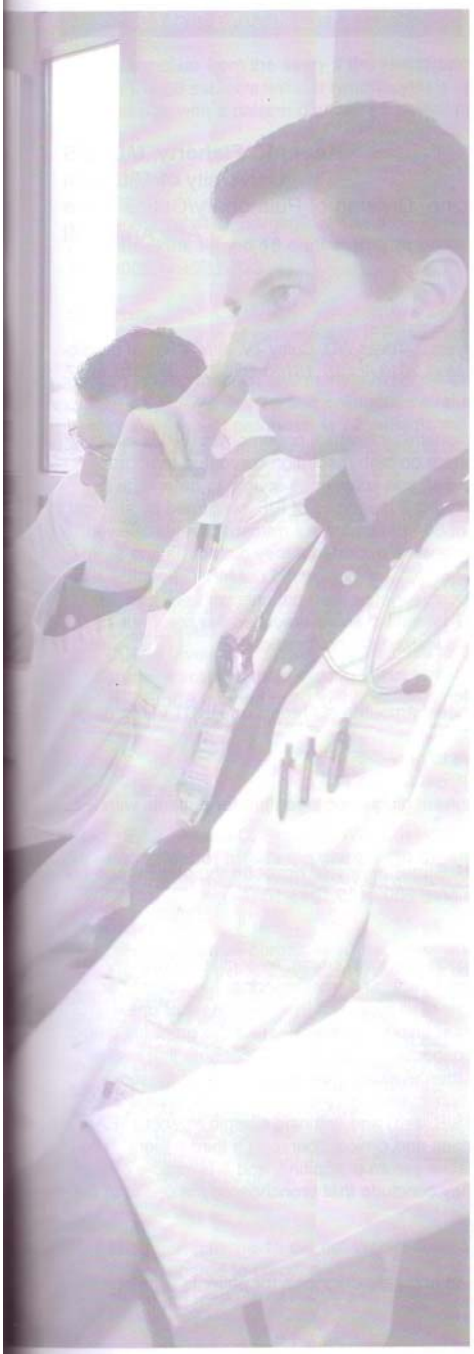

MODERATORS

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La Nouvelle Orleans B-C (Second Level)
Morial Convention Center

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DIAGNOSIS

Fell CD, Martinez FJ, Liu LX, Murray S, Han MK, Kazerooni EA, Gross BH, Myers J, Travis WD, Colby TV, et al. **Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med. 2010 Apr 15; 181(8): 832-7, Epub 2010 Jan 7.*

Summary
Differentiation between idiopathic pulmonary fibrosis (IPF) and non-IPF idiopathic interstitial pneumonias (IIP) is clinically relevant. Patients without a definite usual interstitial pneumonia (UIP) pattern on high resolution computed tomography scan (HRCT) require a surgical lung biopsy for confirmation of diagnosis. Fell and colleagues sought to determine if there was a combination of clinical and HRCT characteristics that could predict a diagnosis of IPF, confirmed by surgical lung biopsy, for patients that lacked a definitive HRCT diagnosis. A total of 664 patients were retrospectively reviewed from the University of Michigan Interstitial Lung Disease database. Patients were excluded if they did not have a surgical lung biopsy, lacked pulmonary function studies and/or HRCT within six months of biopsy, did not have idiopathic disease (i.e. connective tissue disease), or did not have a consensus diagnosis. Ninety-seven patients with IPF and 38 with non-IPF IIPs formed the study group. Increasing age and total HRCT interstitial score predicted the presence of IPF. Pulmonary function, sex, six minute walk test desaturation or distance walked did not predict IPF.

Comments
1. This study highlights the possible role of increasing age and even modest amounts of fibrosis on HRCT in the diagnosis of IPF.
2. There was a high prevalence of IPF in this retrospective study relative to non- IPF IIPs.
3. The applicability of these data to centers with a lower prevalence of IPF is uncertain
4. Prospective validation of these data is required prior to altering the current diagnostic algorithm for patients with IPF.

Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, Costabel U. **Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med* 2009;179:1043-1047

Summary
In 2000 the ATS/ERS published guidelines that outlined four major (exclusion of known cause, restrictive pulmonary physiology with impaired gas exchange, bibasilar reticular abnormalities on HRCT, and transbronchial lung biopsy or lavage not suggesting an alternative diagnosis) and four minor (age greater than 50 years, insidious onset of unexplained dyspnea, duration of illness greater than three months, and bibasilar inspiratory crackles) for the probable diagnosis of IPF without a surgical lung biopsy. Ohshimo and colleagues retrospectively evaluated 74 patients that met all the above criteria without considering the results of bronchoscopy. They then evaluated the results of bronchoscopy which had been performed in all patients and found that 6 (8%) had a lymphocytosis greater than 30% on lavage and the diagnosis is these patients were nonspecific interstitial pneumonia (NSIP, n=3) and extrinsic allergic alveolitis (EAA, n=3). The diagnosis of NSIP was made by surgical lung biopsy in two cases and clinical course in a third patient. The diagnosis of EAA was confirmed by histories of exposure to antigens, relative serum precipitins, and a favorable clinical course after avoidance of antigens and the administration of steroids. They conclude that bronchoscopy is useful in the diagnostic evaluation of patients with suspected IPF.

Comments
1. This study highlights the importance of the clinical history in making an accurate diagnosis for patients with interstitial lung diseases.

2. The lack of a surgical lung biopsy in some of the subjects limits the strength of conclusions regarding final diagnoses.
3. It is unclear from the study if the investigators took into account the clinical course or additional historical information for the 68 subjects without lymphocytosis on BAL.
4. Patients with a pattern of usual interstitial pneumonia on biopsy but an atypical HRCT were excluded.

PROGNOSIS

Prasse A, Probst C, Bargagli E, Zissel G, Toews GB, Flaherty KR, Olschewski M, Rottoli P, Muller-Quernheim J. **Serum cc-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med* 2009;179:717-723

Summary
The clinical course of patients with IPF is variable and predicting prognosis is difficult. Decline in lung function correlates with subsequent risk of mortality *(Am J Respir Crit Care Med 2003; 168:543-8)* although some patients die prior to a decline in lung function and many survive despite declines in lung function *(Chest 2005; 127:171-7, Ann Intern Med 2005;142:936-7)*. Prasse and colleagues evaluated the prognostic ability of serum CC-chemokine ligand 18 (CCL18) to predict subsequent prognosis in 72 patients with IPF. Baseline concentration of CCL18 correlated with six month change in FVC and TLC. Receiver operating characteristic (ROC) analysis revealed a level of 150 ng/ml as the best level to predict a decline in FVC or TLC of 10% or more at six months. This level was also associated with an increased risk of mortality (HR 7.98, 95% CI 2.49-25.51, p=0.0005) using a Cox proportional hazard model which included age, sex, baseline FVC and DLCO, and smoking history.

Comments
1. Prospective validation of these data are required prior to clinical utilization.
2. The lack of a prospective treatment regimen prevents the analysis of any impact on treatment for prognosis or CCL18 level.
3. CCL18 levels could potentially be used to identify a population of patients at risk of disease progression for consideration in clinical trials or lung transplant.
4. The ELISA method used in this study is not standardized so concentrations in this study may not apply to levels obtained in other laboratories.

TREATMENT

King TE, Jr., Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, et al. **Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (inspire): A multicentre, randomised, placebo-controlled trial.** *Lancet* 2009;374:222-228

Summary
Idiopathic pulmonary fibrosis is a fatal disease without definitive therapy. Post-hoc analyses of the first large trial of interferon gamma-1b INF-γ suggested a mortality benefit for patients with mild lung dysfunction *(N Engl J Med 2004;350:125-33)*. The INSPIRE study was a double-blind randomized placebo-controlled multi-center trial of interferon gamma-1b (INF-γ, n=551) versus placebo (n=275). Eligible patients were aged 40-79 years, had been diagnosed within 4 years, had a FVC of 55-90% predicted and a DLCO 35-90% predicted. The primary endpoint was mortality. At the second interim analysis assessment of the primary endpoint from the hazard ratio for mortality in patients treated with INF-g showed absence of minimum benefit compared to placebo (1.15, 95% CI 0.77 – 1.71, p=0.497). The trial was stopped early. At study completion (median treatment duration of 77 weeks) there were no differences between treatment groups in overall survival (85% INF-γ vs 87% placebo), survival without lung transplantation, survival without respiratory-related hospital admission, change in dyspnea, change in six minute walk distance, change in FVC, acute respiratory decompensation, or quality of life.

Comments
1. Interferon gamma-1b did not impact survival or measures of lung function, dyspnea, or quality of life for patients with IPF compared to placebo
2. Interferon gamma-1b should not be used to treat patients with IPF

3. This study highlights the importance of performing prospective trials to validate post-hoc analyses
4. The magnitude of this study demonstrates the need for accurate surrogates of mortality that could be utilized in clinical trials of novel agents for IPF.

OTHER ARTICLES OF INTEREST

TREATMENT

Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR. **Imatinib treatment for idiopathic pulmonary fibrosis: Randomized placebo-controlled trial results.** *Am J Respir Crit Care Med*;181:604-610

Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, et al. **Pirfenidone in idiopathic pulmonary fibrosis.** *Eur Respir J 2010 Apr; 35(4): 821-9, Epub 2009 Dec 8.*

Behr J, Demedts M, Buhl R, Costabel U, Dekhuijzen RP, Jansen HM, MacNee W, Thomeer M, Wallaert B, Laurent F, et al. **Lung function in idiopathic pulmonary fibrosis—extended analyses of the ifigenia trial.** *Respir Res* 2009;10:101

Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S, Cayou C, Shariat C, Collard HR. **Pulmonary rehabilitation in interstitial lung disease: Benefits and predictors of response.** *Chest* 2009;135:442-447

NONSPECIFIC INTERSTITIAL PNEUMONIA

Park IN, Jegal Y, Kim DS, Do KH, Yoo B, Shim TS, Lim CM, Lee SD, Koh Y, Kim WS, et al. **Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia.** *Eur Respir J* 2009;33:68-76

FUNCTIONAL ASSESSMENT

Swigris JJ, Wamboldt FS, Behr J, du Bois RM, King TE, Raghu G, Brown KK. **The 6 minute walk in idiopathic pulmonary fibrosis: Longitudinal changes and minimum important difference.** *Thorax*;65:173-177

HYPERSENSITIVITY PNEUMONIA

Churg A, Sin DD, Everett D, Brown K, Cool C. **Pathologic patterns and survival in chronic hypersensitivity pneumonitis.** *Am J Surg Pathol* 2009;33:1765-1770

GENETICS OF IPF

Konishi K, Gibson KF, Lindell KO, Richards TJ, Zhang Y, Dhir R, Bisceglia M, Gilbert S, Yousem SA, Song JW, et al. **Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis.** *Am J Respir Crit Care Med* 2009;180:167-175

Boon K, Bailey NW, Yang J, Steel MP, Groshong S, Kervitsky D, Brown KK, Schwarz MI, Schwartz DA. **Molecular phenotypes distinguish patients with relatively stable from progressive idiopathic pulmonary fibrosis (ipf).** *PloS one* 2009;4:e5134

CONNECTIVE TISSUE DISEASE RELATED ILD

Marten K, Dicken V, Kneitz C, Hohmann M, Kenn W, Hahn D, Engelke C. **Interstitial lung disease associated with collagen vascular disorders: Disease quantification using a computer-aided diagnosis tool.** *European radiology* 2009;19:324-332

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BRONCHIECTASIS EVALUATION

Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. **Sputum colour: a useful tool in non-cystic fibrosis bronchiectasis.** *Eur Respir J* 2009; 34: 361-364

Summary

In this study, a 29 month prospective cohort study of patients with stable bronchiectasis from Edinburgh Scotland to assess the utility of sputum color in disease assessment. 141 individual patients' sputum samples were graded using a color chart and characterized as mucoid, mucopurulent or purulent. There was good reliability in color interpretation between the doctor and the patient. Sputum color predicted bacterial colonization. There was a 5% rate of bacterial colonization in mucoid sputum, 43.5% in mucopurulent sputum and 86.4% in purulent sputum. The most common organisms found in the purulent sputum samples were H. influenza (n=21) and pseudomonas aeruginosa (n=15). Purulent sputum was independently associated with varicose or cystic bronchiectasis, forced vital capacity less than 80% predicted and diagnosis of bronchiectasis at less than 45 years of age. The authors concluded that sputum color may be a useful adjunct to clinical management while awaiting microbiology results.

Comments

1. This study lends credence to a common clinical practice.
2. Sputum color analysis should be viewed as an adjunct but not a substitute for bacterial culture.
3. Sputum purulence (in the stable patient) may also be a marker of disease severity.

BRONCHIECTASIS EVALUATION

Montella S, Santamaria F, Salvatore M, Pignata C, Maglione M, Iacotucci P, Mollica C. **Assessment of chest high field magnetic resonance imaging in children and young adults with noncystic fibrosis chronic lung disease: comparison to high-resolution computed tomography and correlation with pulmonary function.** *Invest radiol* 2009; 44:532-538

Summary

In this study from Naples, Italy, 41 subjects with non-CF chronic lung disease underwent high field magnetic resonance imaging (MRI), high resolution CT scanning (HRCT) and a subset also had pulmonary function testing in order to determine the effectiveness of MRI compared to HRCT in assessing extent of lung disease and relationship to lung function. The subjects ranged in age between 5.9 and 29.3 years (median 13.8) and had primary ciliary dyskinesia, primary immunodeficiency or recurrent pneumonia. MRI was done with a 3.0T MR scanner; HRCT with a 4 slice CT scanner. The authors found good agreement in MRI and HRCT scores, using a modification of the scoring system developed by Helbich et al for cystic fibrosis. The bronchiectasis scores also correlated with pulmonary function tests. The authors concluded that chest high field 3.0T MRI appears to be as effective as HRCT in imaging bronchiectasis. MRI scanning is radiation free and well tolerated and may have a role in patients with bronchiectasis.

Comments

1. This is the first study to evaluate high-field 3.0T MRI in bronchiectasis compared to the "gold standard" HRCT imaging
2. It is particularly relevant given concerns regarding excessive radiation exposure from serial CT scanning in patients with chronic benign disease.
3. The 3.0T MRI scanner is not universally available in clinical practice at this time.

4. Breath holding/respiratory gating is a limitation of MRI scanning for lung disease.
5. The authors suggest that MRI scanning may ultimately have a role in following patients with bronchiectasis after an initial baseline HRCT in order to reduce radiation exposure.

BRONCHIECTASIS OUTCOMES

Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, Wilson R. **Mortality in bronchiectasis: a long-term study assessing the factors influencing survival.** *Eur Respir J* 2009; 34: 843-849

Summary

This study analyzed the factors that predicted mortality in a cohort of 91 bronchiectasis patients followed at the Royal Brompton Hospital, London UK, over a 13 year period. The subjects had baseline assessment for etiology of bronchiectasis, pulmonary function testing, high resolution CT scanning, sputum microbiology and quality of life scores. 29.7% of the patients died during the 13 year follow up period. Multivariate analysis showed that baseline St George's Respiratory Questionnaire activity score, pseudomonas aeruginosa infection, total lung capacity, residual volume/total lung capacity and transfer factor coefficient were associated with mortality. 20 of the 27 deaths were directly due to bronchiectasis; the median age of death was 60 years. The authors conclude that lung function measurements at baseline in addition to age, pseudomonas infection and health status measured by questionnaire are important in assessing prognosis in bronchiectasis.

Comments

1. This study shows that multiple factors impact the outcome in bronchiectasis.
2. This study's major limitation is that it was perfomed in a single, very specialized tertiary care center.
3. The authors correctly highlight the heterogeneous nature of patients with bronchiectasis, the variable natural history, and hence the difficulty in planning endpoints for clinical trials. Subsets of patients may need to be studied in order to best assess outcomes of new treatments.

BRONCHIECTASIS THERAPY

Gursoy S, Ozturk AA, Ucvet A, Erbaycu AE. **Surgical management of bronchiectasis: indications and outcomes.** *Surg Today* 2010;40:26-30

Summary

This study reports the outcomes of 92 bronchiectasis patients treated surgically at the Izmir Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, Izmir,Turkey. There were 54 female and 38 male patients with average age of 38.7 years. Recurrent or childhood infections were the most frequent cause of bronchiectasis. 10 pneumonectomies were performed; the rest of the patients had lobectomies and or segmentectomies or combined procedures. The authors reported a 16% morbidity rate and 1% mortality over a 15.3 month follow up period. In the 75 patients with follow up data, 84% were asymptomatic, 10.7% were improved and 5.3% of patients reported no clinical improvement. The authors concluded that surgery is a reasonable option in selected patients with bronchiectasis.

Comments

1. The findings here are similar to other surgical series of patients with bronchiectasis
2. There are multiple caveats: single center study, young patients, selection bias, self reported improvement.
3. Despite all of those caveats, this paper adds to the evidence that surgery does have a role in selected patients with bronchiectasis.

Chang KC, Leung CC, Yew WW, Lau TY, Leung WM, Tam CM, Lam HC, Tse PS, Wong MY, Lee SN, Wat KI, Ma YH. **Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis?** *Eur Repir J* 2009 Aug 28 (Epub ahead of print)

Summary

This randomized, open-label controlled trial of 427 patients in Hong Kong with community acquired pneumonia or bronchiectasis exacerbation was designed to determine if newer fluroquinolone therapy for respiratory infection masks tuberculosis. Patients were assigned by randomized permutated blocks of 20 to receive either amoxicillin clavulanate or

moxifloxacin for five days as treatment of their community acquired respiratory infection and then were monitored for one year for development of active pulmonary tuberculosis. Three participants were found to have positive mycobacterial cultures at entry and were excluded from analysis. Of the remaining subjects, 10 of 210 who received amoxicillin/clavulanate (8 of 10 culture positive) and three of 214 who received moxifloxacin developed active pulmonary tuberculosis (2/3 culture positive). The authors concluded that the lower rate of active TB in the moxifloxacin treated patients suggests that active pulmonary tuberculosis is being masked by the fluroquinolone therapy.

Comments

1. This study raises concerns regarding the masking of TB and possible delay of treatment in an endemic area by the use of short course fluroquinolone therapy for bacterial pneumonia and bacterial exacerbations of bronchiectasis.
2. This study shines a light on the potential risks of empiric courses of antibiotics for bronchiectasis patients who may have unrecognized mycobacterial tuberculosis infection or non-tuberculous mycobacterial infections.
3. Fluroquinolones (and macrolides) should be used judiciously in patients with bronchiectasis. Routine mycobacterial surveillence may be appropriate in patients with bronchiectasis.

OTHER ARTICLES OF INTEREST

BRONCHIECTASIS: PATHOPHYSIOLOGY AND CLINICAL FEATURES

King, PL. **The pathophysiology of bronchiectasis.** Intern J COPD 2009; 4:411-419

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BRONCHIECTASIS: TREATMENT

Abanses JC, Arima S, Rubin B. **Vicks Vaporub induces mucin secretion, decreases ciliary beat frequency and increases tracheal mucus transport in the ferret trachea.** *Chest* 2009; 135: 142-148

MacLeod DL, Barker LM, Sutherland JL, Moss SC, Gurgel JL, Kenney TF, Burns JL, Baker WR. **Antibacterial activities of a fosfomycin/tobramycin combination: a novel inhaled antibiotic for bronchiectasis.** *J Antimicrob Chemother* 2009; 64: 829-836

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MEDICARE COVERAGE FOR PULMONARY REHABILITATION

Centers for Medicare and Medicaid. **Payment and coverage improvements for patients with chronic obstructive pulmonary disease and other conditions – pulmonary rehabilitation services.**
Physician fee schedule: *Federal Register*, November 25, 2009; vol 74, No.226: pages 61879-86
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Summary

The absence of consistent, uniform coverage policies for pulmonary rehabilitation (PR) has severely limited access and availability of these services for many patients with chronic lung diseases. After many years of concerted and cooperative effort by professional organizations (including ATS, ACCP, AARC, AACVPR, and NAMDRC), in 2008 the US Congress passed legislation directing Medicare (CMS) to establish a national coverage policy for PR. CMS regulations were released in 2009 and the coverage became effective on January 1, 2010. These new regulations provide for PR coverage for patients with moderate to very severe COPD under a new bundled CPT code (G0424) and, for the time being, continuation of existing coverage for other pulmonary diseases by local Medicare contractors. The new code covers up to 36 sessions of PR that must include exercise in addition to other PR components, and allows two 1-hour sessions per day. Another 36 sessions may be allowed based on clinical need. The new rules also require significant physician involvement and documentation of outcomes. Although all of the details of this new policy have not yet been worked out with Medicare contractors, this new, national benefit for PR under Medicare is clearly a major step forward in increasing PR coverage for many eligible patients in the United States.

Comments

1. Consistent coverage for PR has been a major barrier in limiting access for many patients with chronic lung diseases.
2. After many years of effort, a new, Congressionally mandated Medicare (CMS) national coverage policy for PR was implemented on January 1, 2010.
3. This new benefit should allow expansion of PR benefits to many more eleigible patients.
4. Active physician involvement in PR is an essential component of the new coverage policy.

PULMONARY REHABILITATION GUIDELINES

Ries AL, Bauldoff FS, Carlin BW, Casaburi R, Emery CP, Mahler DA, Make B, Rochester CL, ZuWallack R, Herrerias C. **Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines.** *Chest* 2007; 131:4S-42S.

Summary

Pulmonary rehabilitation (PR) has become a standard of care for patients with chronic lung diseases based on a growing body of scientific evidence. This comprehensive guideline provides a systematic review of the published literature and updates and expands the prior guidelines published in 1997. The new evidence strengthens the previous recommendations supporting the benefits of exercise training and improvements in dyspnea and health-related quality of life from PR. Additional evidence supports improvements in health-care utilization and psychosocial outcomes. Some new evidence idnicates that longer term PR, maintenance strategies following initial PR, and the incorporation of education and strength training in PR are also beneficial. Other topics covered include inspiratory muscle training (not recommended routinely), anabolic drugs, nutritional supplementation, supplemental oxygen, noninvasive ventilation, and PR for patients with chronic lung diseases other than COPD.

Comments

1. There has been substantial growth in the body of scientific evidence supporting the use of PR as a standard of care for patients with chronic lung diseases.
2. Evidence-based guidelines have been important in justifying proposals to third party payors and regulators to expand coverage for PR for these patients.
3. Evidence-based guidelines can be helpful for clinical programs in developing appropriate evaluation methods to document benefits of PR and positive outcomes from their program.
4. Evidence-based guidelines also help to identify important areas for future research.

SIX MINUTE WALK TEST IN PULMONARY REHABILITATION

Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. **Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease.** *Arch Phys Med Rehabil* 2010; 91:221-5.

Summary

Measurement of exercise tolerance is an important outcome from pulmonary rehabilitation (PR) in patients with chronic lung diseases. The six-minute walk distance (6MWD) is used commonly in such programs, in the absence of more formal laboratory cardiopulmonary exercise tests. Despite its widespread use, the minimal important difference (MID) for the 6MWD is not well established. An MID of 54 meters is cited commonly based on one previous study (Redelmeier et al). However, more recent evidence suggests that a lower value for the MID of the 6MWD may be more appropriate, especially in patients with moderate to severe COPD. Holland and coworkers utilized both anchor-based and distribution-based methods to determine the MID for the 6WMD in 75 patients with COPD participating in a 7-week PR program. Results from the anchor-based methods identified the MID as 25 meters (95% CI = 20-61m). This corresponded closely with results from distribution-based methods of 26 meters. These results add to the growing body of evidence that the commonly cited value of 54 meters for the MID of the 6MWD may be too high and underestimate clinically important changes from PR in such patients.

Comments

1. Despite its widespread use in both clinical and research settings, the MID for the 6MWD test is not well established.
2. A growing body of evidence suggests that the commonly cited MID of 54 meters for the 6MWD is too high for patients with moderate to severe COPD.
3. Using both anchor-based and distribution-based methods, this study suggests that 25 meters is a more appropriate value for the MID of the 6MWD.
4. Use of the commonly cited value of 54 meters may significantly underestimate the benefits of PR in patients with chronic lung disease.

PULMONARY REHABILITATION IN RESTRICTIVE LUNG DIESASE

Salhi B, Troosters T, Behaegel M, Joos G, Derom E. **Effects of pulmonary rehabilitation in patients with restrictive lung diseases.** *Chest* 2010; 137:273-9.

Summary

Most of the evidence documenting benefits from pulmonary rehabilitation (PR) has been obtained in studies of patients with COPD, the most common types of chronic lung diseases. Patients with other types of chronic lung diseases have similar problems with limited exercise tolerance and impaired quality of life that also could benefit from PR. However, such patients have not been studied as systematically largely due to the fewer number of eligible patients. Given the expansion of coverage for PR and greater availability of such programs, it will be important to justify inclusion of the non-COPD patients who might otherwise be denied these potential benefits. This prospective, observational study evaluated the effectiveness of a 24-week outpatient PR program for 31 patients with restrictive lung diseases (11 with interstitial lung diseases) in Belgium. Results demonstrated significant improvements in symptoms and exercise capacity that were similar and, in some cases, exceeded those typically observed in patients with COPD. Also, as in other studies in COPD, these results confirmed that longer PR treatment was more effective in maintaining benefits than the typical short-term PR treatment. This study confirms others that patients with restrictive lung diseases are also good candidates for PR.

Comments

1. Most studies establishing the benefits from PR have been performed in patients with COPD.
2. Principles of PR can be applied equally to patients with chronic lung diseases other than COPD, but such studies are difficult to perform since such diseases are less common.
3. Results of this prospective, observational study confirm the fact that PR for patients with restrictive lung diseases produces benefits similar to those observed in patients with COPD.

4. The study also confirms the observation that longer PR treatment results in better long-term maintenance of benefits than the typical short-term treatment.
5. Patients with chronic lung diseases other than COPD should be considered for PR, although the treatment program needs to be tailored to their individual needs.

PULMONARY REHABILITATION EFFECT ON LUNG FUNCTION

Stav D, Raz M, Shpirer I. **Three years of pulmonary rehabilitation: inhibit the decline in airflow obstruction, improves exercise endurance time, and bocy-mass index, in chronic obstructive pulmonary disease.** *BMC Pulmonary Med* 2009; 9:26-30.

Summary

Pulmonary rehabilitation (PR) has been well documented to improve symptoms, exercise tolerance, and health-related quality of life in patients with chronic lung disease, but does not result in improvement in lung function. However, most studies of PR in patients with COPD have examined outcomes from relatively short-term intervention. Stav and coworkers evaluated the efficacy of a 3-year outpatient PR program in 80 patients with COPD in a matched control study design. PR subjects received supervised outpatient sessions twice weekly and instructed to carry out exercise an additional two days per week at home. Control subjects received no exercise training or PR intervention. In the 67 subjects who completed the 3-year study, results demonstrated not only improvement in maximum and endurance exercise performance in the PR versus control subjects, but also less decline in FEV1 (74 ml in PR versus 149 ml in controls). These intriguing results suggest that continued PR treatment may, in fact, slow the decline in lung function in patients with COPD. If confirmed, these findings not only provide an additional, important justification for PR as a disease modifying treatment, but also emphasize the importance of a longer-term treatment model.

Comments

1. Pulmonary rehabilitation produces important health benefits for patients with COPD but has not been shown to improve lung function.
2. Although most studies of PR have involved short-term intervention, longer-term treatment may be associated with improved long-term outcomes.
3. This intriguing study is the first to suggest that longer-term PR treatment may, in fact, modify the course of disease and reduce the rate of decline in lung function.
4. If confirmed, these results provide an important new justification for PR and suggest that a different, longer-term treatment model may be appropriate.

OTHER ARTICLES OF INTEREST

Clini EM, Crisafulli E, Costi S, Rossi G, Lorenzi C, Fabbri LM, Ambrosino N. **Effects of early inpatient rehabilitation after acute exacerbation of COPD.** *Respir Med* 2009; 103:1526-31.

Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. **Interpretation of treatment changes in 6-minute walk distance in patients with COPD.** *Eur Respir J* 2008; 32:637-43.

Rasekaba TM, Williams E, Hsu-Hage B. **Can a chronic disease management pulmonary rehabilitation program for COPD reduce acute rural hospital utilization.** *Chron Respir Dis* 2009; 6:157-63.

Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. **Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients.** *Am J Respir Crit Care Med* 1997; 155:1278-82.

Spencer LM, Alison JA, McKeough ZJ. **Maintaining benefits following pulmonary rehabilitation: a randomised controlled trial.** *Eur Respir J* Jul 30. [Epub ahead of print].

Van Wetering CR, Hoogendoorn M, Mok SM, Rutten-van Molken MP, Schols AM. **Short- and long-term efficacy of a community-based COPD management program in less advanced COPD: a randomized controlled trial.** *Thorax* 2009 Aug 23 [Epub ahead of print].

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CHRONIC CRITICAL ILLNESS

Cox CE, Martinu T, Sathy SJ, Clay AS, Chia J, Gray AL, Olsen MK, Govert JA, Carson SS, Tulsky JA. **Expectations and outcomes of prolonged mechanical ventilation.** *Crit Care Med.* 2009 Nov;37(11):2888-94.

Summary
Patients who develop chronic critical illness (CCI) are at high risk for death or long-term functional impairment. Because many patients would rather be allowed to die than endure profound debilitation and dependency, it is important for physicians to discuss with surrogate decision-makers in ICUs the likely outcomes of chronic critical illness when making decisions about ongoing use of life sustaining treatments. Cox and colleagues sought to prospectively determine long-term outcomes of a cohort of 126 patients receiving prolonged mechanical ventilation at an academic medical center, the amount of communication about prognosis, and the accuracy of surrogates' perceptions of the likely outcomes of treatment. At 1 year follow-up, only 9% of the cohort was alive and functionally independent. 93% of surrogates reported high expectations for 1 year survival, compared to 43% of physicians. 71% of surrogates reported high expectations for good long-term functional outcomes compared to 6% of physicians. 74% of surrogates reported that physicians did not discuss the outcomes of treatment with them during the decision-making process about ongoing intensive care.

Comments
1. Long-term outcomes of patients with CCI were exceedingly poor, with only 9% being alive and free from severe functional impairment at 1 year follow-up.
2. Both physicians and surrogates were overly optimistic about the likely outcomes of patients with chronic critical illness.
3. Neither physicians nor surrogates were particularly accurate in predicting outcomes, though physicians were more accurate than surrogates.
4. The data highlight the need for accurate risk prediction models for CCI that physicians and surrogates can use to inform their decisions making.
5. The data also suggest that there may be deficiencies in disclosure of prognostic information to surrogates.

CONFLICT IN ICUs

Azoulay E, Timsit JF, Sprung CL, et al.; Conflicus Study Investigators for the Ethics Section of the European Society of Intensive Care Medicine. **Prevalence and factors of intensive care unit conflicts: the conflicus study.** *Am J Respir Crit Care Med.* 2009 Nov 1;180(9):853-60. Epub 2009 Jul 30.

Summary
Intensive care units are complex social environments where multidisciplinary collaboration is required. Although many sources of conflict exist in ICUs, little is known about the prevalence, characteristics, and risk factors for conflict. Azoulay and colleagues therefore conducted a 1-day cross sectional survey of 7498 ICU staff members from 323 ICUs in 24 countries. 72% of respondents reported conflict within the week prior to the survey, with 53% rating the conflicts as severe. Nurse-physician, nurse-nurse, and clinician-family conflicts were the most common types. Multivariate analysis identified 6 factors associated with conflict that may be amenable to intervention, including high work volumes, absence of multi-disciplinary meetings in ICUs, and insufficient support for the emotionally challenging care of dying patients. Higher levels of conflict were associated with more perceived job strain.

Comments

1. This study quantifies that conflict, in many forms, is prevalent in ICUs.
2. It reminds us that the social complexity of ICUs may impact patient care, staff moral and burnout.
3. The association between the level of conflict and job strain raises the possibility that interventions to improve staffs' conflict resolution skills may be warranted.

CONFLICT AND END OF LIFE CARE IN ICUs

Fine RL. **The Texas Advance Directives Act effectively and ethically resolves disputes about medical futility.** *Chest* 2009; 136;963-67.

Truog R. **The Texas advance directive act is ethically flawed.** *Chest.* 2009 Oct;136(4):968-71.

Summary

Disputes are common in ICUs about whether ongoing treatment is "futile". Truog and Fine examine the ethics of the Texas Advance Directives Act (TADA), a dispute resolution process sanctioned by law in Texas for cases in which physicians think ongoing use of life sustaining treatment is inappropriate. The TADA delineates a 7-step process for clinicians who wish to withdraw life sustaining treatment over the objections of a surrogate. This decision-making mechanism is noteworthy because it gives sole authority to physicians and hospital ethics committees to make moral judgements about when it is appropriate to discontinue life support. It does not permit cases to be appealed to courts and provides legal immunity to physicians who adhere to the 7-step process. Fine argues that decisions about whether ongoing treatment is inappropriate are ultimately technical medical judgments that should be made by the medical community without appeals to other authorities, such as judges or communities of citizens. Truog argues that decisions about what constitutes inappropriate treatment hinge on value judgements, which the medical community is not well positioned to decide alone. He cites as reasons the lack of diversity and expertise on many ethics committee, as well as and the potential conflicts of interest that arise on institutional ethics committees. He proposes an alternative multi-step approach that balances medical expertise with the option of substantive appeal to the courts in intractable cases.

Comments

1. The TADA raises moral and policy questions about how much authority physicians and hospital ethics committees should have to determine whether extending an individual patient's life is ethically wrong.
2. Truog and Fine implicitly frame the question differently: is the appropriateness of ongoing intensive treatment a purely clinical judgement or one that can be influenced by diverse cultural, religious, and moral beliefs?
3. Although the TADA mechanism is efficient, there are concerns that it puts complex life or death decisions in the hands of individuals who may not be well positioned to make such decisions, without the potential for oversight or appeal.
4. The TADA also raises larger questions about who determines the appropriate ends of medicine—clinicians alone or in clinicians in collaboration with society?

SURROGATE DECISION MAKING

White DB, Malvar G, Karr J, Lo B, Curtis JR. **Expanding the paradigm of the physician's role in surrogate decision-making: an empirically derived framework.** *Crit Care Med.* 2010;38(3):743-50.

Summary

Surrogate decision making in ICUs is common, difficult, and understudied. White and colleagues conducted a multicenter study to characterize the roles physicians take in the decision-making process. They audiotaped physician-family meetings involving 496 surrogates and 414 clinicians and developed a coding framework to identify physicians' roles in life support decisions. 65% of the time, physicians used 1 of 3 roles previously described in the medical literature: the informative role (12%), in which the physician only provides information about the patient's condition, prognosis, and treatment options, but does not elicit the patient's values, engage in deliberations, or provide a recommendation about whether to continue life support; the collaborative role (51%) in which the physician provides relevant medical facts but also elicits the patient's values and provides a treatment recommendation; and the directive role (1%), in which the physician assumed all responsibility for, and informed the family of, the decision. The authors also describe a novel role called the facilitative role which was used by 35% of physicians, in which the physician refrained from providing a recommendation and instead actively guided the surrogate through a process of clarifying the patients' values and applying those values to the decision at hand. Many clinicians moved through several roles during a single meeting. However, in half of the meetings in which surrogates requested a recommendation, the physician refused to provide one.

Comments

1. There is considerable variability in the roles physicians take in decision-making about life support with surrogates but little negotiation of desired roles.
2. The most commonly cited models of the physician-surrogate relationship—informed decision-making, shared decision-making, and paternalism—do not adequately describe practice.
3. The facilitative role provides a middle ground for physicians who have concerns about providing a recommendation, but who also wish to assist surrogates in the decision-making process.
4. These data suggest that communication training for physicians in ICUs should focus less on learning and adhering to one approach to decision-making and more on teaching clinicians techniques to discern surrogates' needs and then adapt their approach to meet these needs.

OTHER ARTICLES OF INTEREST

IMPACT OF COMMUNICATION ON PATIENT, SURROGATE, AND SOCIETAL OUTCOMES

Zhang B, Wright AA, Huskamp HA, Nilsson ME, Maciejewski ML, Earle CC, Block SD, Maciejewski PK, Prigerson HG. **Health care costs in the last week of life: associations with end-of-life conversations.** *Arch Intern Med.* 2009 Mar 9;169(5):480-8.

Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, Volicer L, Givens JL, Hamel MB. **The clinical course of advanced dementia.** *N Engl J Med.* 2009. 361(16): p. 1529-38.

Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, Mitchell SL, Jackson VA, Block SD, Maciejewski PK, Prigerson HG. **Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment.** *JAMA.* 2008 Oct 8;300(14):1665-73.

RELIGIOSITY AND END OF LIFE CARE

Phelps AC, Maciejewski PK, Nilsson M, Balboni TA, Wright AA, Paulk ME, Trice E, Schrag D, Peteet JR, Block SD, Prigerson HG. **Religious coping and use of intensive life-prolonging care near death in patients with advanced cancer.** *JAMA.* 2009 Mar 18;301(11):1140-7.

SURROGATE DECISION MAKING

White DB, Evans L, Bautista C, Luce JM, Lo B. **Are physicians' recommendations to limit life support beneficial or burdensome? Bringing empirical data to the debate.** *Am J Respir Crit Care Med.* 2009 Aug;15:180(4):320-5.

Evans LR, Boyd EA, Malvar G, Apatira L, Luce JM, Lo B, White DB. **Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty.** *Am J Respir Crit Care Med.* 2009 Jan 1;179(1):48-53. Epub 2008 Oct 17.

Zier LS, Burack JH, Micco G, Chipman AK, Frank JA, White DB. **Surrogate decision makers' responses to physicians' predictions of medical futility.** *Chest.* 2009 Jul;136(1):110-7. Epub 2009 Mar 24.

Thornton JD, Pham K, Engelberg RA, Jackson JC, Curtis JR. **Families with limited English proficiency receive less information and support in interpreted intensive care unit family conferences.** *Crit Care Med.* 2009 Jan;37(1):89-95.