出國報告(出國類別：參加國際會議)

# 2013 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、上校主任
派赴國家：美國費城
報告日期：102 年 5 月 31 日
出國時間：102 年 5 月 15 日至 5 月 24 日

## 壹、 摘要：

急性肺損傷 (acute lung injury, ALI) 爲臨床上常見嚴重急症，有極高的死亡率。當肺泡受到感染時，嗜中性白血球會大量遷移到肺部組織，毒殺外來物質，但發炎物質亦會傷害肺臟組織，嚴重時會造成急性呼吸窘迫症候群 (acute respiratory distress syndrome, ARDS) 致死。研究指出，急性肺損傷病患的體內往往承受著過多的發炎物質及氧化壓力。因此，降低發炎反應及氧化壓力是治療急性肺損傷的一個有利方向。 Dextromethorphan 是 NMDA 接受器的抑制劑，在臨床上是已使用多年的治療咳嗽藥物，文獻中指出，Dextromethorphan 具有抗發炎和抗氧化的功效。本研究目的主要在探討內毒素誘導肺損傷模式中，評估給予 Dextromethorphan 是否有保護效果並探討相關機制。本實驗設計爲於實驗前一小時投予 Dextromethorphan (20 mg/kg, i.p.)，之後再於氣管內滴入內毒素 (5 mg/kg)，並，在第 6 小時將動物犧牲及評估肺損傷程度。實驗結果顯示，Dextromethorphan 可顯著減少支氣管肺泡灌洗液中蛋白質濃度、白血球數目、細胞激素 (tumor necrosis factors-α, TNF-α；intreleukine-1β, IL-1β；intreleukine-6, IL-6) 及趨化激素 (macrophage inflammatory, MIP-2)，且可減少肺組織中肺組織濕/乾重量比、骨髓過氧化酶 (myeloperoxidase, MPO) 活性，並降低 COX-2 蛋白質表現量。同時，也明顯改善肺臟病理組織變化。此外，本實驗也發現 Dextromethorphan 顯著減少肺組織中 NFκB 表現量。因此，我們推論 Dextromethorphan 可能是經由減少細胞激素、趨化激素釋放與降低發炎性基因表現及自由基生成以及降低 NF-κB 的轉錄作用，顯著減少肺組織中 ROS 含量及抑制肺組織 iNOS、 XBP1、 ASK1、 p38、 CHOP 等表現，但可增加 HO-1 和 GRP78 基因表現 caspase-3 蛋白質表現量減少，降低細胞走向細胞凋亡路徑。因此，推論 Dextromethorphan 減少細胞激素、趨化激素釋放與降低發炎性基因表現及自由基生成，增加 GRP78 基因表現，使內質網壓力相關因子及細胞凋亡被抑制，而達到療效。

2013 年美國胸腔學會年會(2013 American Thoracic Society Annual meeting)再費城舉辦。此學會是胸腔界最重要的盛會，在各領域包含癌症、呼吸生裡、基礎醫學轉譯、急重症照護醫學、睡眠醫學、外科移植等橫跨基礎及臨床等所有議題，期宗旨在提供在職教育鼓勵研究交流。併提供胸腔疾病最佳照護模式及最新的知識，American Journal of Respiratory and critical care medicine 即爲其最重要的出版刊物俱有 High Impact Factor

這個年會 2013 ATS annual meeting 對胸腔內外科基礎及臨床的專業人士及所有會員是最具代表性的盛會。很榮幸有機會以海報發表方式將近幾年之研究成果發表於此次會議中。研究主題是探討 Dextromethorphan 對於內毒素所誘發肺損傷之保護作用。

# 參加 2013 年美國胸腔國際會議出國報告目錄

## 貳、 本文：

**(一)目的：**參加美國胸腔學會國際會議主要的目的是展示“探討 Dextromethorphan (DM) 對於內毒素所誘發肺損傷之保護作用”，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進一步研究議題。並且參加研究課程且吸收新知的動向。期望對於肺癌、急性呼吸窘迫症、肺臟移植及急性肺損傷的生物標記有進一步的認識及瞭解。

**(二)過程：**

2013 年 5 月 15 日晚上搭乘長榮航班經洛杉磯，芝加哥轉機於 5 月 16 日下午抵達美國費城。入住旅館後，稍事休息，隨即趕往會場領取會議資料，仔細研讀議程並安排順序挑選重要且個人有興趣的題目，準備認真學習併更新相關領域最新知識。

會議第一天(5 月 17 日)

早上 8 點準時到達會場參加臨床應用心生物標記診斷及處理診斷及處置呼吸及重症疾病研討會，此研討會由 K.A Crothers seattle.WA. A.Caffamanchr.Jan Francisco.CA 及 C.A Hage.Indianapolis 主持。生物標記的評估牽涉證實、量化及應用三步驟。K.A.Crothers 提到有各種不同型式的 Biomarker. 必須有準確性重複及穩定的特性，單次的測量就有代表的意義。可以區分出正常及疾病的狀況，容易解讀可以用來解釋部分疾病的結果。

在運用 Biomarker 診斷及治療細菌性肺炎方面 N.C.Dean 提出 procalcitonin 的濃度於肺炎及敗血症產生時會升高。 procalcitonin 可以作爲使用或停用抗生素的參考。可以減少治療失敗率但不會減低死亡率。

下午 T.E west 演講生物指標對敗血症的診斷和管理，敗血症的病理生理機制很複雜，對敗血症的診斷是具有挑戰性的，實際上沒有最適合敗血症的生物指標，最好的敗血症生物指標尚未被信賴，以多種生物指標/組織學方式，可能最有前景，敗血症的生物指標，仍有許多發現以待驗證。

最後一場，C.S.lalfee 演講生物指標如何使用在 ARDS 的病理機制，在臨床面臨 ARDS 時，尚未使用生物指標，生物指標（ANG-2）可預測高危險因子的病患會發生 ARDS 的機率，利用生物指標診斷對 ARDS 病程的危險度可用於正確分級，P/ F 比值（生理性的生物指標），目前正用於危險分層在臨床試驗和治療方式，使用生物指標作爲治療終點，須小心謹慎，往後數年生物指標洞察發病機制，許多指標測試在臨床試驗室是缺乏的/在做法上是一個主要的障礙。

會議第二天(5 月 18 日)

參加 2013 年肺癌晶點研討會由 M.P.Rivera.chapel Hill.及 D.J.Feller-Kopran 主持。Dr.D.E.Dst 於 The solitary pulmonary nodule: when do we need to do something 中提到，孤立性肺結節是一個常見的問題且能呈現診斷的困境，支氣管鏡檢採樣率是 70%左右，準確率提高對存在的支氣管徵象和結節的大小，支氣管鏡採樣時併發症發生率低與氣胸發生率在 1%左右，提高診斷率和確定因素，需要更多進步的技術與嚴謹的研究。

接下來於 Tissue acquisition 及 Specimen processing: optimizing Histological and Molecular characterization of Lung Cancer. 主題中 Dr.D.J.Feller-kopman 總結 Histological Subtyping 及 mutation analysis 於處理非小細胞肺癌是很關鍵及重要的步驟於肺腺癌基因檢測 EGFR,KRAS 及 ACK-1 是必要的腫瘤科病理科及胸腔內外科專家間的無障礙溝通對於分子分析及診斷很重要。大部分非小細胞肺癌無法手術，晶支氣管鏡超音波導引採樣是比較無侵入性及能切片供分子診斷及分析的子見，本院尚無此設備，建議早日採購。

於 The Biology of Lung Cancer: update and clinical Implication.C.A.powell 結論提及診斷肺癌的生物標記的發現。証實及運用耗時耗力尚未完全適合臨床運用。對於晚期侵犯性強的肺線癌基因的檢測對於 TKI 及 Crizotinib 是標準的治療模式。我們本院在這方面也作的很好能跟上世界潮流。對於 Biotechnology 及 Bioscience 發現新肺癌的標記尚須進一步臨床的証實。現在用微創途徑如 EBUS-TBNA 取得的切片以足夠作 Biomarker 的 assays.本院應即早建置 EBUS-TBNA 及 ROSE program.

會議第三天(5 月 19 日)

於廠商展示區參觀新產品展示，美國胸腔學會很用心，新產品的設計橫跨基礎及臨床也包括各類新藥品的展示，其中 EBUS-TBNA. Navigation bronchoscopy. Thermoplasty treating Bronchial Asthma 以及用 One Way Valve 作 Bronchoscopic Lung volume reduction surgery 是重點產品。肺癌標靶治療藥物及 COPD 新開發抗發炎及治療哮喘的藥物也日新月異配合呼吸領域新書的發表讓人目不暇給。希望這些新東西能盡早引進台灣以造福病患。

會議第四天(5 月 20 日)

早上 8:45 準時參加 clinical year in Review 由 E.R.sutherlard. H.R.collurd 及 R.O.stapleron 所主持此會場高朋滿座座無空席。E.A.Kazeroon 在 Radiology section 提到關於 Lung Cancer Screening Fleischer Society 建議 GGN 小於 5mm 不需要再追蹤 >5mm 3 個月用胸部電腦斷層再追蹤一次要持續 3 年。GGN>5mm 有 solid component 要立刻切片和以外科手術後取得切片證實及排除惡性的可能性。對於多數 pure GGNS<5mm 也建議追蹤 2 到 4 年。本院也是符合世界潮流以相同方式追蹤及處置病人。

會議第五天(5 月 21 日)

今天是 ATS meeting 的重頭戲，我一早就到會場張貼海報，會場的擺置讓人震撼，雖然有上千份海報張貼，但併不覺得擁擠，我的海報是探討 Dextromethorphan 對於 Lipopolysaccharide 引起急性肺損傷的保護作用。

RID Hubmayr 及 A.Kapoor 二位座長詢問何時該給藥及用多少劑量?他們認爲我們這個題目很新穎，結果豐碩。對於機轉的討論深入，對於往後治療急性肺損傷不是單純的給予抗生素也許預防性的投予 Dextromethorphan 是不錯的選項，也有些學者建議可以使用不同動物肺損傷的模式再度證實預防性給藥的效用。

上午接受很多來自不同國家的學者提問感覺收獲良多。中間利用空檔時間在回到商品展覽場操作及熟悉尖端的機械手臂運用於肺及食道切除的技巧，此技術兼顧

3D 放大實體影像及能運用靈活 360 度機械手臂切除及分離組織的特性。本院明年將引進新款，這是未來微創手術必然的趨勢。

下午參加 new England Journal of medicine 及 JAMA 主編的研討會學習併參觀爲何 clinical Trial 及 Translation medicine 文章如何刊出在此國際知名的期刊，併了解到 clinical Trial 困難之處。

下午也參加了預防及提早治療急性肺損傷準則及觀念改變的研討會由史丹福大學 J.E.Levitt 及波士頓的 B.T.Thompson 主持的研討會，舊金山大學醫學院的 C.S.Calfee 在生物指標在認定及區分及治療急性肺損傷的發生時間，她的研究團隊發現 angiopoietin-2 此種生物指標可以預估及判斷病患者產生急性肺損傷的時間，經多次校正後 angiopoietin-2 預測 ALI 還是很準確。Angiopoietin-2 可以幫助預防及提早治療急性肺損傷。

## (三)心得：

1. 討論重點觀注於術前或受傷後給藥並於那個時間點給藥
2. 有人也尋問肺損傷呼吸機所扮演調控的機制到底是否使用低潮氣呼吸及正壓的模式或是只使用高潮氣呼吸容積造成肺損傷?
3. 分子的致病機轉及下一步研究方向也是被尋問重點
4. 2013 年會討論到急性肺損傷及呼吸窘迫症有 4 篇文章是大家所關注的，由 Carolyns. calfee 學者提出討論

1. New definition of ARDS. Acute respiratory Distress syndrome: The Berlin Defintion.JAMA.2012 Jun20;307123:2526-33 由 Ranserivm 及 slutsky As 等所提出新的 Berlin ARDS 定義須急性發作，$PaO_2/FiO_2$<300 雙側 bilateral radiographic opacity mild (P/F ratio 200-300). moderate (P/F ratio 100-200).Severe(P/F ratio ≤100)併排除 Acute Lung injury 用詞。P/F ratio 須再使用 PEEP 及 5cm $H_2O$ CPAP 狀況下測量 moderate 及 severe form 須插管併於 PEEP=5 cm $H_2O$ 下測急性發作定義症狀發生內一星期。
2. Mouse models of inflammatory disease seok J.es al Genomic responses in mouse model poorly mimic Human inflammatory diseases proc nat Acad scv 2013 Feb 雖然許多新的治療方式於 mouse model 有用，但於 human clinical trials 證明是失敗的。問題出在於 mouse model 及 clinical trials 沒有類似的狀況。作者比較 gene expression pattern in peripheral blood leukocytes 於 Trauma, severe burns 及 experimental endotoxemic between patients 及 C57BL16 mice 這個發現也與 global analyses of change in gene expression 及分析 specific pathways 一致，但此研究僅專注於 leukocyte gene expression 改變並沒描述 protein product. Gene expression on target organs or patho-physiology 的相似度。
3. Long term outcomes
   Need ham DM etc. Lung protective mechanical Ventilation and two year survival in patients with acute Lung injury: prospective cohort study. BMJ2012 Apr 5:344:e2124
   這個研究收集四大醫學中心 485ARDS 病患(C/F ratio <300)以 low tidal volume strategy 觀察 ARDS 發作後二年內死亡率只有 41%病患呼吸機設定遵照 lung protection ventilation. Low tidal volume ventilation 減少 3%死亡率。Mean tidal volume >8.5me/kg 死亡率增加 2 倍。ARDS 二年內死亡率大約 64%和 age., Comorbidities ,number of organ failure, fluid balance 相關。
4. High frequency Oscillatory Ventilation Ferguson ND, etc
   High frequency Oscillation in early acute respiratory distress syndrome N Engl J med.2013 Jan 22
   高速震動通氣(HF00)使用 1-2cc/kg 之潮汐通氣、氣道壓力高，呼吸次數每分 3-15 次主要作用能接上肺泡反覆通氣及關閉。Oscillate triage 隨機將 54%AR 嚴重病患分配接受 HFOV 及傳統 Tidal volume < 6 me/kg. plateau pressure≤35cm water 併使用 high PEEP in hospital mortality.

HFVO=47% control group=35%,P=0.005 治療效果二組沒差異，病患使用 HFOV 需要較大量 Vasopressors 及 Neuromuscular blockade 及高劑量 midazolam

## (四)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。
3、針對肺癌標靶治療希望盡快引進 Crizotinib for treating EML4-ALK gene mutation 的患者。
4、引進高解析度更低劑量快速胸部電腦斷程掃描，對於高危險群病患的篩檢能夠有效降低肺癌死亡率。
5、呼出氣體中的新生物標記是診斷急性肺損傷慢性阻塞性肺部疾病及肺癌未來的研究方向，能做爲治療的參考及判斷預後存活率的重要指標。
6、肺門高壓從基礎到臨床的研究越來越熱門，配合藥物的開發近年內有很大的進展，國內需要大規模的臨床研究併開發適合東方自己國人的藥物。
7、支氣管內皮細胞切片早期肺癌篩檢配合大規模基因檢測，是未來研究重要重點 。

投稿摘要如下

# The Protective Effect of Dextromethorphan on Lipopolysaccharide-induced Lung Injury in Rats

H. Chang[1], J.J. Ru[2], C.T. Chong[2], L.S. Chung[1];
[1]Tri-Service General Hospital - Taipei/TW, [2]National Defense Medical Center - Taipei/TW

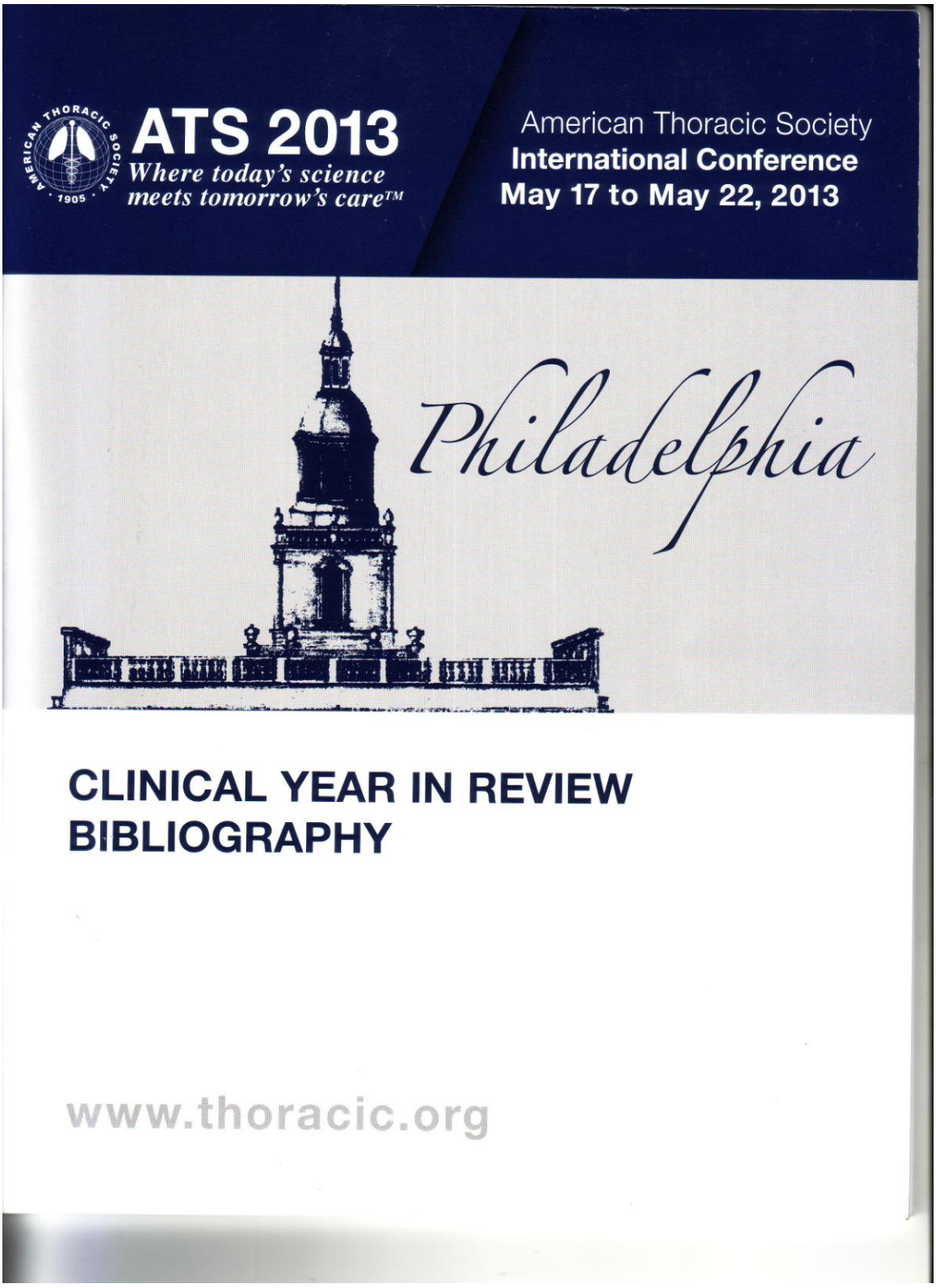
**Purpose:**
Acute lung injury (ALI) includes the impairment of the alveolar-capillary barrier, with the accumulation of protein rich fluid and influx of inflammatory cells into the alveolar airspace, and associates with pulmonary cells damage. Dextromethorphan (DM), a non-competitive *N*-methyl -D-aspartate receptor antagonist, is widely used anti-tussive drug. DM has been reported to exert anti-inflammatory effect against tissue injury in endotoxemia rats. The aim of this study was to investigate the effects of the DM on LPS-induced lung injury, and further elucidated the involved mechanism.

**Materials and Methods:**
We used intratracheal (i.t.) instillation lipopolysaccharide (LPS)-induced ALI in rats, and evaluated the prevention effects of DM. Rats were given intraperitioneal injections of DM (20,50 mg/kg) 1 h before intra-tracheal injection of LPS (2mg/kg) and sacrifice at 6 hour later. We use ELISA and myeloperoxidase activity to determine that DM significantly suppressed pro-inflammatory cytokines (tumor necrosis factor-alpha,interleukin-1β and interleukin-6) and free radicals (hydrogen peroxide) in bronchoalveolar lavage fluid (BALF). NF-κB translocation and nitrotyrosine was assessed by immunofluorescence and immunohistochemical. The ER stress protein expression was assessed by western blotting.

**Results:**
DM significantly attenuated the symptoms of ALI, reflected by attenuation of Wet/dry ratio of the lungs, protein concentration and number of total WBC counts in bronchoalveolar lavage fluid (BALF) accompanied with the lung pathological changes. In addition, DM significantly decreased myeloperoxidase activity and the levels of superoxide and nitrite/nimate in lung tissue, and alleviated LPS-induced the production of tumor necrosis factor-receptor alpha (TNF-α), interleukin (IL)-6, IL-1β, macrophage inflammatory protein-2 in BALF, as well as cyclooxygenase-2 and inducible nitric oxide synthase expression. Furthermore, the increased phosphorylation level of NF-κB p65 in ALI was inhibited by DM. In addition, DM significantly diminished ROS formation and inhibited iNOS, XBP1, ASK1, p38, CHOP, caspase-3 gene expression but upregulated HO-1, GRP78 expression in lung tissue, accompanied by reduced apoptosis.

**Conclusion:**
DM exerts a beneficial effect in LPS-induced lung injury through decrease of proinflammatory mediators formation, but enhancement of GRP78 gene expression, subsequently leading to attenuation of apoptosis. Additionally, DM diminished ER stress-medicated CHOP induction and caspase-3 activation, but upregulated GRP78 expression in lung tissue.

參. 附錄：參加會議之資料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## MOLECULAR CHARACTERIZATION

Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, Luo X, Wang L, Li H, Zhang Y, Li F, Lu Y, Lu Q, Xu J, Garfield D, Shen L, Ji H, Pao W, Sun Y, Chen H. **RET Fusions Define a Unique Molecular and Clinicopathologic Subtype of Non-Small-Cell Lung Cancer.** *J Clin Oncol*. 2012 Dec 10;30(35):4352-9.

### Summary

The discovery of "driver kinases" in lung cancer has revolutionized our understanding and therapy of lung cancer. This is further reinforced with the identification of a new fusion gene in lung cancer, RET fusions. RET (rearranged during transfection) is a receptor tyrosine kinase involved in cell proliferation, neuronal navigation, cell migration and cell differentiation. RET activation occurs in multiple endocrine neoplasia type 2 (medullar thyroid cancer, pheochromocytoma, and hyperparathyroidism). This study of 936 NSCLCs in a Chinese population identifies the clinical characteristics of NSCLC that have this fusion. RET fusions occurred only in adeno- or adeno-squamous carcinomas with a prevalence of 1.7%. Clinically, patients were predominantly never smokers, younger, and had small primary lesions but typically had advanced disease (N2) when compared to adenocarcinomas without RET fusions. The cancers were poorly differentiated and had no other driver mutations. A RET fusion predicted worse relapse free survival than an EGFR or ALK mutation (20.9m vs. 28.4m vs. 26.9m respectively) but was better than a KRAS mutation (12.3m). Due to the small cohort size the survival differences were not statistically significant.

### Comments

1. This study adds to known driver kinases in lung cancer.
2. This work continues to support the differences in clinical phenotype, mechanisms of tumor development, and targeted therapies between lung cancers in smokers versus non-smokers.
3. The clinical phenotype seen with RET fusions is younger, never-smoker, adenocarcinoma histology, and exclusive of other driver mutations, but predictive of a more aggressive pathologic phenotype (N2 disease).
4. There are clear differences in ethnic background associated with the frequency of driver mutations in lung cancer and the frequency of this mutation in a Caucasian population needs to be defined.
5. Therapy targeting RET fusions with crizotinib is possible and its efficacy in these cancers needs to be explored.

## PLEURAL DISEASE

Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YC, Davies RJ, Miller RF, Rahman NM. **Effect of an Indwelling Pleural Catheter vs. Chest Tube and Talc Pleurodesis for Relieving Dyspnea in Patients with Malignant Pleural Effusion: the TIME2 Randomized Controlled Trial.** *JAMA*. 2012 Jun 13;307(22):2383-9.

### Summary

The Second Therapeutic Intervention in Malignant Effusion Trial was an unblinded randomized controlled trial that directly compared indwelling pleural catheter (IPC) vs. chest tube and talc pleurodesis (CT) in 106 patients with malignant pleural effusion (breast, lung, mesothelioma, other). At 42 days after intervention there was no difference in dyspnea between the two groups, though there was significant improvement from baseline. Chest pain, 1-year survival, and global quality of life were also not significantly different. However, at 6 months there was a clinically and statistically significant difference in dyspnea favoring the IPC group. A larger, though not significant, proportion of IPC patients were admitted for drain related complications, but spent less time in the hospital than the CT group. There were more adverse events in the IPC group (40% vs. 13%) but there was no difference in serious adverse events. Of the CT group, 22% required further pleural procedures vs. 6% of the IPC group. 57% of the IPC group had their catheter removed and fluid recurred in 3 patients giving an overall spontaneous pleurodesis rate of 51%.

### Comments

1. This is the first randomized prospective trial comparing IPCs with CT and talc slurry pleurodesis.
2. Both approaches are equivalent in relieving dyspnea as initial symptom relief for malignant pleural effusions.
3. Though not powered to directly test secondary outcomes, IPC had a significant improvement in dyspnea at 6 months, a significant reduction in further pleural interventions needed over 12 months, fewer hospital days, but more drain related complications.
4. Treatment choice should be guided by a patient's concerns about hospitalization, home care, and potential adverse events.

## RISK STRATIFICATION

Kratz JR, He J, Van Den Eeden SK, Zhu ZH, Gao W, Pham PT, Mulvihill MS, Ziaei F, Zhang H, Su B, Zhi X, Quesenberry CP, Habel LA, Deng Q, Wang Z, Zhou J, Li H, Huang MC, Yeh CC, Segal MR, Ray MR, Jones KD, Raz DJ, Xu Z, Jahan TM, Berryman D, He B, Mann MJ, Jablons DM. **A Practical Molecular Assay to Predict Survival in Resected Non-Squamous, Non-Small-Cell Lung Cancer: Development and International Validation Studies.** *Lancet*. 2012 Mar 3;379(9818):823-32.

### Summary

Adjuvant therapy in Stage I lung cancer has not shown a survival benefit perhaps due to heterogeneity of patients with or without occult disease. Gene signatures to identify a "high-risk" subgroup have been reported, but are limited due to a need for fresh tissue, lack of independent laboratory and blinded validation, single institution accrual, and limited ethnic groups. In this study the authors developed an expression signature of 14 genes that assigned a lung cancer mortality risk using RNA extracted from formalin-fixed, paraffin embedded, non-squamous cell lung cancer tissue (NSqCLC). Based on their risk score, patients were broken into three groups of differing mortality (high, intermediate, low). This signature was validated in an independent laboratory using a community cohort of 433 Stage I (Kaiser Permanente Northern California) and 1006 Stage I-III NSqCLC patients (China Clinical Trials Consortium). The signature predicted 5-year lung cancer specific survival in the community cohort (Stage I, 84.6%, 70.32% and 63.3%) and all stages of the Chinese cohort; Stage I= 83.0%, 67.7%, 64.6%, Stage II 54.2%, 45.8%, 38.1%, and Stage III 53.3%, 43.3%, 24.0%. The high risk category had a HR of 2.37 (1.63-3.43, P<0.001) and the intermediate group had a HR of 1.60 (1.03-2.49, P=0.0354).

### Comments

1. This is the first gene expression signature using RNA extracted from FFPE tissue, with testing performed in an independent CLIA certified laboratory, and validated in large cohorts of differing ethnic backgrounds for lung cancer prognosis.
2. Similar findings within a diverse ethnic background suggest that there are fundamental elements that can characterize NSqCLC independently of a particular genetic makeup.
3. The genes used in the prognostic algorithm fit with our understanding of the biology of lung cancer, especially adenocarcinomas.
4. Tests like this may provide guidance, especially in low stage disease, as to who may benefit from adjuvant therapy.
5. Prospective validation is needed.

## SQUAMOUS CELL CARCINOMA PATHOGENESIS

Rogers, Kristen [corrected to Rodgers, Kristen]. Cancer Genome Atlas Research Network. **Comprehensive Genomic Characterization of Squamous Cell Lung Cancers.** *Nature*. 2012 Sep 27;489(7417):519-25. Erratum in: *Nature*. 2012 Nov 8;491(7423):288.

### Summary

Mutations in the epidermal growth factor receptor and fusions involving anaplastic lymphoma kinase have led to new treatment options for patients with lung adenocarcinomas. Our understanding of the mutational landscape in squamous cell carcinomas (SCC) is not as developed. This study begins to fill that knowledge gap. Tumor samples were obtained from 178 patients with untreated stage I-IV SCC. Comparison germline DNA was obtained from "normal" lung tissue resected at surgery or from peripheral blood nucleated cells. Using a number of different platforms the investigators identified;

1. On average, 228 potentially significant exon mutations per tumor.
2. An average somatic mutation rate of 8.1 mutations/Mb which is significantly higher than what is seen in many other cancers; breast=1.0/Mb, ovarian=2.1/Mb, colorectal 3.2/Mb.
3. Gene mutations that were identified made biologic sense and included TP53, CDKN2A, PTEN, PIIK3CA, KEAP1, MLL2, HLA-A, NFE21.2, NOTCH1, RB1 with secondary analyses identifying HRAS, EGFR, BRAF, APC.
4. Many of the mutations could be drivers of important pathways; oxidative stress response (34%), squamous differentiation (44%).
5. By matching the identified mutations to available FDA approved targeted therapeutic agents, or agents in clinical trials, 64% of the cases had a potentially targetable gene for therapy.

### Comments

1. Lung SCC is characterized by a high mutation rate.
2. There appears to be a common dysfunction in cell cycle control, response to oxidative stress, apoptotic signaling and squamous cell differentiation in SCC.
3. An alteration in HLA-A that would lead to loss-of-function was identified which is the first time such a change has been reported in lung cancer and may represent a way that tumor cells escape immune detection.
4. EGFR and KRAS mutations were rare, unlike adenocarcinomas, while FGFR alterations were common making SCC genetic alterations similar to head and neck carcinomas.
5. These studies do not address function of the mutations and whether they are "driver mutations" that could be targeted with clinical effect as with *EGFR* and *ALK* in lung adenocarcinomas.

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## NEW DEFINITION OF ARDS

ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. **Acute Respiratory Distress Syndrome: The Berlin Definition**. *JAMA*. 2012 Jun 20;307(23):2526-33.

### Summary

ARDS is a syndrome defined by consensus, prior to this publication by the 1994 American-European Consensus Conference (*AJRCCM* 1994). In 2011, a group of investigators assembled in Berlin to re-consider the definition of ARDS. A draft definition was proposed and subsequently evaluated using data from nearly 4,500 patients enrolled in clinical research studies. The new definition preserves the essence of the prior definition: specifically, the acute onset of a PaO2/FiO2 ratio < 300 and bilateral radiographic opacities thought to be due primarily to non-cardiac causes. It defines three classes of ARDS: mild (P/F ratio 200-300), moderate (P/F ratio 100-200), and severe (P/F ratio ≤ 100) and eliminates the term "acute lung injury." In addition, it stipulates that patients with mild ARDS must have their P/F ratio measured while on either PEEP or CPAP of at least 5 cm water, and those with moderate or severe ARDS must be intubated and have their P/F ratio measured on at least PEEP of 5. It defines "acute onset" as onset within one week of a known clinical insult or development of symptoms. It recommends objective assessment of cardiac function using echocardiography if a known clinical risk factor for ARDS is not present.

### Comments

1. The new "Berlin definition" of ARDS preserves the central features of the prior AECC definition while clarifying several aspects of the diagnostic criteria, including timing, findings on chest imaging, and the origin of the edema.
2. The new definition makes explicit the clinical observation that ARDS often co-exists with hydrostatic pulmonary edema by requiring only that respiratory failure is not *fully* explained by cardiac failure or fluid overload.
3. While radiographic severity, low respiratory compliance, high positive end-expiratory pressure, and high minute ventilation were initially proposed as part of the new definition of severe ARDS, analysis of patient data revealed that they did not contribute additional predictive value to the P/F ratio, and these criteria were therefore discarded.
4. The Berlin definition had a modestly improved predictive value for mortality compared to the AECC definition (area under the receiver operating curve 0.58 vs 0.54, p<0.001); however, as the authors emphasize, this improvement is not likely to be clinically significant, and the definition is not intended for use as a predictive tool.
5. The Berlin definition does not address classification of patients with an ARDS-like clinical syndrome who are not mechanically ventilated, which may limit its applicability to early or incipient ARDS and to clinical and research use in resource-limited settings.

## HIGH-FREQUENCY OSCILLATORY VENTILATION

Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO; the OSCILLATE Trial Investigators and the Canadian Critical Care Trials Group. **High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome**. *N Engl J Med*. 2013 Jan 22. [Epub ahead of print]

### Summary

High-frequency oscillatory ventilation (HFOV) is a mode of mechanical ventilation that uses very small tidal volumes of 1-2 cc/kg delivered at a relatively high mean airway pressure and an extremely rapid rate (3-15 breaths/second), with the goal of optimizing alveolar recruitment while minimizing repetitive alveolar opening and closing. Several small studies suggested that treatment of adult patients with ARDS with HFOV might improve clinical outcomes; however, many of these studies were conducted prior to the era of lung-protective ventilation. The OSCILLATE trial randomized patients with moderate or severe ARDS (P/F ratio ≤ 200 on an FiO2 of ≥0.5) within 72 hours of onset of ARDS to either HFOV or a conventional ventilation group (pressure control ventilation, tidal volume target 6 ml/kg, plateau pressure ≤ 35 cm water, relatively high levels of PEEP). Both groups underwent a recruitment maneuver at baseline. The trial was terminated on the recommendation of the Data Safety Monitoring Committee after 548 patients had been randomized. In-hospital mortality, the primary outcome of the study, was 47% in the HFOV group, compared with 35% in the control group (relative risk of death with HFOV compared to control, 1.33; p=0.005). There was no evidence that the treatment effect differed in patients with more severe ARDS. Patients treated with HFOV required vasopressors and neuromuscular blockade more frequently than those in the control group; the HFOV patients also required higher doses of midazolam.

Young D, Lamb S, Shah S, Mackenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH; the OSCAR Study Group. **High-Frequency Oscillation for Acute Respiratory Distress Syndrome**. *N Engl J Med*. 2013 Jan 22. [Epub ahead of print]

### Summary

Like the OSCILLATE trial, the OSCAR trial randomized patients with moderate to severe ARDS to either HFOV or a conventional ventilation strategy. Eligibility criteria included a P/F ratio of ≤ 200 on PEEP of ≥ 5 cm water and the expectation that the patient would require at least 2 more days of mechanical ventilation. The study protocol encouraged but did not mandate ventilation for patients in the control arm with pressure controlled ventilation, using a goal tidal volume of 6-8 ml/kg and conventional levels of PEEP. The trial enrolled 795 patients (target sample size 802 patients). Mortality at 30 days was 41.7% in the HFOV group and 41.1% in the conventional ventilation group (p=0.85). There was no difference in ventilator-free days between the two groups. As in the OSCILLATE trial, use of neuromuscular blockade was more prevalent in the HFOV group; likewise, there was a trend towards a longer duration of sedative usage in the HFOV group (8.5 ± 6.9 days in conventional ventilation vs. 9.4 ± 7.2 days in HFOV, p=0.07). In contrast to the OSCILLATE trial, there was no significant difference between the groups in the duration of usage of vasopressors or inotropes. Other differences between the two studies included the use of a different mechanical ventilator and slightly different protocols to deliver HFOV and the lack of a recruitment maneuver in this trial. No subgroup analysis by severity was reported.

### Comments

1. Taken together, these two studies indicate that the routine use of HFOV in patients with moderate to severe ARDS is not beneficial and may in fact be harmful.
2. The negative effects of HFOV may be due to high intra-thoracic pressures, which may have caused more ventilator-associated lung injury and resulted in higher vasopressor and/or fluid resuscitation requirements, and/or the requirement for increased use of sedatives and neuromuscular blockade.
3. The mean airway pressures in HFOV-treated patients were generally higher in the OSCILLATE trial compared to the OSCAR trial, as a result of the design of the ventilation protocols, which may partially explain some of the differences in these two trials.
4. The control arm in both trials was treated with a ventilator strategy that differed in some ways from the protocol initially proven effective in the landmark ARDS Network low tidal volume study.

## LONG-TERM OUTCOMES

Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Dennison Himmelfarb CR, Desai SV, Shanholtz C, Brower RG, Pronovost PJ. **Lung Protective Mechanical Ventilation and Two Year Survival in Patients with Acute Lung Injury: Prospective Cohort Study**. *BMJ*. 2012 Apr 5;344:e2124.

### Summary

Mortality in the months to years after hospital discharge is high among critical care survivors, including among patients with ARDS. Interventions that improve short-term outcomes (e.g. 28-day survival) may not translate into long-term survival benefit. This observational study of 485 ARDS patients (P/F ratio < 300) enrolled at four academic centers between 2004-2007 determined the association between ventilation with a low tidal volume strategy and mortality at 2 years after ARDS onset. Ventilator settings were captured twice per day for all patients. Only 41% of ventilator settings were classified as "adherent to lung protective ventilation" (tidal volume ≤ 6.5 ml/kg predicted body weight, and plateau pressure ≤ 30 cm water), and 37% of patients had no ventilator settings compatible with low tidal volume ventilation. Mortality at 2 years after ARDS onset was 64% and was independently associated with age, comorbidities, number of organ failures, and fluid balance, among other factors. After adjusting for other predictors of survival, the risk of death over two years decreased by 3% for each additional ventilator setting adherent to lung protective settings (p=0.002). The risk of two-year mortality for patients ventilated with a mean tidal volume of > 8.5 ml/kg was nearly double that of patients ventilated with a mean tidal volume of < 6.5 ml/kg, adjusted for other predictors (hazard ratio 1.97; 95% CI 1.23-3.16; p=0.004).

### Comments

1. Despite widespread consensus that a lung protective strategy is the optimal approach to ventilating patients with ARDS, many patients with ARDS were not ventilated according to the low tidal volume protocol that was demonstrated to be effective several years prior to this observational study.
2. The survival benefit associated with lower tidal volumes in this study appears durable; however, lung protective ventilation in this study could also be a marker for other quality process of care variables that influence patient outcomes.
3. The study did not assess whether the survival benefit of lower tidal volume ventilation accrues only during hospitalization or increases after discharge.
4. More efforts to disseminate and facilitate implementation of the findings of landmark clinical trials in critical care are needed.

## MOUSE MODELS OF INFLAMMATORY DISEASE

Seok J, Warren HS, Cuenca AG et al. **Genomic Responses in Mouse Models Poorly Mimic Human Inflammatory Diseases**. *Proc Nat Acad Sci* 2013 Feb 11 [Epub ahead of print]

### Summary

While many novel therapeutics have successfully treated ARDS, sepsis, and other severe inflammatory conditions in mouse models, very few novel therapeutic agents have demonstrated success in human clinical trials of similar conditions. This provocative new study suggests that one reason for the negative results of so many clinical trials is the lack of similarity between mouse models and the human conditions they are trying to model. The authors compared gene expression patterns in peripheral blood leukocytes from patients with trauma, severe burns, or experimental endotoxemia to those from the corresponding mouse models, using C57BL/6 mice. Gene expression changes were extremely similar in humans with trauma compared to humans with severe burns, and moderately similar in humans with experimental endotoxemia; in contrast, gene expression changes were only marginally correlated between humans and mouse models for each condition. This finding was consistent in both more global analyses of changes in gene expression and analysis of specific pathways. The authors also analyzed gene expression data from publicly available datasets of patients with sepsis and/or ARDS and corresponding mouse models, with similar findings.

### Comments

- This article challenges one of the fundamental approaches to identifying new therapies for severe inflammatory states, including sepsis and ARDS, by suggesting that mouse models of these diseases may often be poor substitutes for the human conditions.
- The study focused only on leukocyte gene expression changes and did not address differences in protein products, gene expression in target organs, or other metrics of pathophysiologic similarity.
- The sample size for human endotoxemia and for the mouse models of disease was small, and further replication will be needed.
- This study underscores the need for additional experimental and clinical human studies designed to illuminate the biology of severe inflammatory conditions, including ARDS.

## OTHER ARTICLES OF INTEREST

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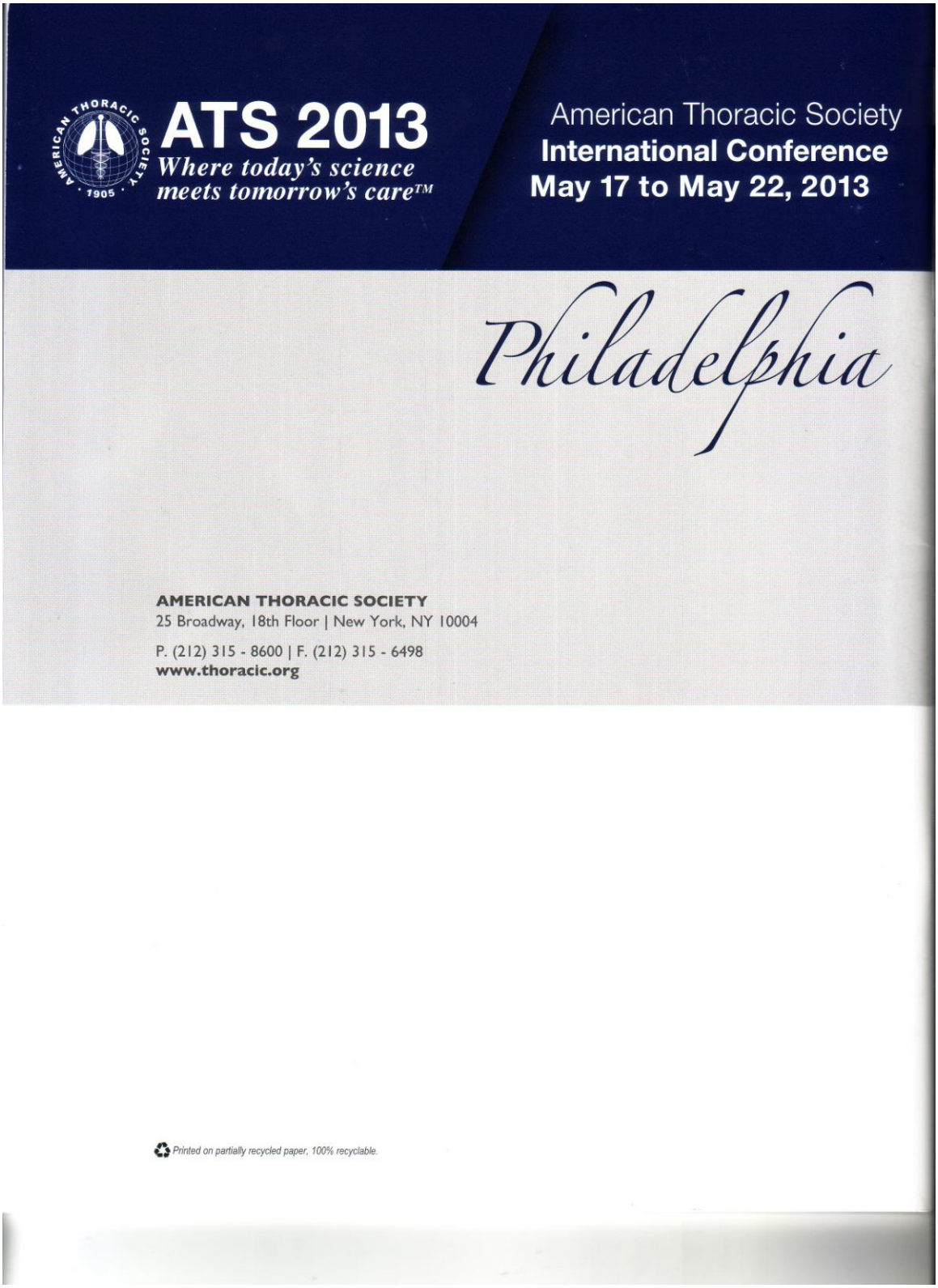
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