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Association of pre-hospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients

Daryl J. Kor, MD, Jason Erlich, MD, Michelle N. Gong, MD, Michael Malinchoc, MS, Rickey E. Carter, PhD, Ognjen Gajic, MD, and Daniel Talmor, MD on behalf of US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG–LIPS)

Abstract

Objective—To evaluate the association between pre-hospitalization aspirin therapy and incident acute lung injury in a heterogeneous cohort of at-risk medical patients.

Design—This is a secondary analysis of a prospective multicenter international cohort investigation.

Setting—Multicenter observational study including 20 US hospitals and 2 hospitals in Turkey.

Patients—Consecutive, adult, non-surgical patients admitted to the hospital with at least one major risk factor for ALI.

Interventions—None.

Measurements and Main Results—Baseline characteristics and ALI risk factors/modifiers were identified. The presence of aspirin therapy and the propensity to receive this therapy were determined. The primary outcome was ALI during hospitalization. Secondary outcomes included intensive care unit (ICU) and hospital mortality and ICU and hospital length of stay. Twenty-two hospitals enrolled 3,855 at-risk patients over a 6-month period. Nine hundred and seventy-six (25.3%) were receiving aspirin at the time of hospitalization. Two hundred and forty (6.2%) patients developed ALI. Univariate analysis noted a reduced incidence of ALI in those receiving aspirin therapy (odds ratio = 0.65; 95% CI = 0.46 to 0.90; $p = 0.010$). This association was attenuated in a stratified analysis based on deciles of ASA propensity scores (Cochran-Mantel-Haenszel pooled odds ratio = 0.70; 95% CI = 0.48 – 1.03; $p = 0.072$).

Conclusions—After adjusting for the propensity to receive aspirin therapy, no statistically significant associations between pre-hospitalization aspirin therapy and ALI were identified; however, a prospective clinical trial to further evaluate this association appears warranted.

Keywords

Acute Lung Injury; Acute Respiratory Distress Syndrome; Aspirin; Prevention

Address correspondence requests to (no reprints available): Daryl J. Kor, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Telephone: 507-255-6051 / Fax: 507-255-4267, kor.daryl@mayo.edu.

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Introduction

Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are life-threatening critical care syndromes with limited treatment options. Despite numerous promising therapies in preclinical studies (1–5), translation to clinical benefit has been elusive. Alternatively, the identification of effective prevention strategies may prove more effective in addressing this serious condition. However, with the exception of lung protective ventilation strategies (6–8) and conservative transfusion practices (8–10), effective preventative interventions are also lacking.

Platelet activation has been linked to numerous biologic processes beyond hemostasis such as inflammatory reactions, vascular permeability, and altered immune function (11, 12). Accumulating evidence also suggests an active role for platelets in both ALI pathogenesis (13–15) and resolution (16–18). Pre-clinical data suggests that aspirin (ASA) can modulate many of the platelet-mediated processes involved in ALI development (15, 19, 20) and resolution (21, 22). We recently confirmed a potential preventative role for anti-platelet therapy in patients at high risk for ALI (23). However, this investigation had several important limitations as the study population was homogenous and it was performed in a single academic medical center.

The objective of the current investigation was to further define the association between pre-hospitalization ASA therapy and the development of ALI in a heterogeneous population of patients at high-risk for ALI with appropriate adjustment for potentially confounding variables. We hypothesized that in this more diverse study population, pre-hospitalization ASA therapy would remain associated with a reduced incidence of ALI/ARDS.

Materials and Methods

This is a secondary analysis of a multicenter, prospective cohort investigation. The prospective study was approved by the Institutional Review Board at each participating institution. Approval was also granted for ancillary studies such as the present investigation. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in the design and reporting of this observational study (24).

Study Population

Details of the study population have been previously described (25). Briefly, consecutive adult patients were enrolled prospectively in 19 hospitals and retrospectively (after hospital discharge) in 3 hospitals over a 6-month period, beginning in March 2009. Participating institutions included both community and academic medical centers. Twenty of the included hospitals were located in the US with two additional institutions located in Turkey. Inclusion criteria consisted of admission to the hospital with the presence of at least one major risk factor for ALI and age > 18 years. Variables considered major risk factors for ALI included aspiration, pneumonia, sepsis, shock, pancreatitis, high-risk trauma or high-risk surgery. For the present investigation, surgical patients were excluded due to the frequent discontinuation of anti-platelet agents before elective surgery and an inability to reliably determine the presence or absence of ASA therapy at the time of hospital admission. The remaining risk factors needed to be present at the time of hospital admission to be considered. Standardized definitions were used to identify these risk factors [high-risk trauma (26, 27), aspiration (26, 28), sepsis (11, 29), shock (29, 30), pneumonia (26, 29), and pancreatitis (29, 31)]. Cardiogenic shock was not included as a major risk factor for ALI and was not sufficient for inclusion in this study. Patients were excluded if they presented to the hospital with ALI (prevalent ALI), if they were transferred from an outside hospital, died in the emergency

department (ED), or were admitted for comfort or hospice care. Hospital readmissions during the study period were also excluded.

Predictor variables

The exposure of interest was ASA therapy at the time of hospital admission. ASA therapy was defined as documentation of use or administration of any ASA-containing medication at the time of hospital admission in the medical record. Baseline characteristics, including demographics, comorbidities, and other clinical characteristics were also collected during the first 6 hours after initial emergency department evaluation by review of the study participant's medical record. ALI/ARDS risk factors and potential risk modifiers were extracted and the predicted risk of ALI was determined using the Lung Injury Prediction Score (LIPS) (25). This validated score weighs the following variables to calculate a predicted risk of developing ALI while in the hospital: aspiration, pneumonia, sepsis, shock, high-risk surgery, high-risk trauma, alcohol abuse (32, 33), obesity (body mass index [BMI] > 30) (34), hypoalbuminemia (26, 35) chemotherapy (36, 37), $\text{FiO}_2 > 35\%$ (38), tachypnea ($\text{RR} > 30$) (26, 36), $\text{SpO}_2 < 95\%$, acidosis ($\text{pH} < 7.35$) (26), and diabetes mellitus (only in patients with sepsis) (26, 39). Standardized definitions were used to identify these variables (see Appendix 1, supplemental online digital content). Allocation of the presence of ASA therapy and additional variables of interest was performed by a member of the study staff at each participating institution. Investigators and study coordinators at each site reviewed the studies' standard operating procedures and received structured online training for definitions of each risk factor prior to study initiation. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was recorded as a measure of severity of illness. In the three hospitals that collected data retrospectively, the investigators followed the same protocols and definitions, but data were collected after hospital discharge.

Outcome Variable

The primary outcome was development of ALI or ARDS during the hospitalization. Standard American-European consensus conference (AECC) (40) criteria were used for determination of ALI and ARDS. Specifically, in order to be allocated a diagnosis of ALI, the following elements were required: development of acute, bilateral pulmonary infiltrates on chest radiograph, a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 (≤ 200 for ARDS), and absence of signs for left atrial hypertension as the main explanation for pulmonary edema. All of these diagnostic criteria needed to be present during the same 24-hour epoch to meet criteria for ALI. The adjudication of ALI/ARDS diagnoses were made locally at each participating site by a member of the study team. Investigators and study coordinators at each site underwent a structured on-line tutorial for the assessment of ALI prior to study initiation. Secondary outcome measures included ICU and hospital mortality, and ICU and hospital length of stay.

Statistical analysis

Assuming a baseline ALI frequency of 6.2% and a 25% rate of ASA administration (data from the study population), the sample size required to identify an odds ratio of 0.5 with ASA administration was calculated to be 2194 (two-sided $\alpha = 0.05$, $\beta = 0.20$). For comparisons of putative prognostic factor between participants that received ASA and those that did not, standard descriptive and inferential methods were used. Dichotomous variables are presented as counts with percentages. Continuous data are presented as median with 25% to 75% interquartile ranges (IQR). Comparisons between the two groups were performed with a Pearson's χ^2 test or Fisher's exact test as appropriate for categorical variables. Continuous variables were tested with the Mann-Whitney rank-sum test and the Kruskal-Wallis Test, as appropriate. To further evaluate the association between ASA therapy and lung injury, a sensitivity analysis was performed assessing the association between ASA and ARDS (cases only meeting criteria for ALI were excluded).

Observational studies risk unequal distributions of important covariates between treatment groups since random assignment is not used. Thus, a propensity score analysis was performed. The propensity score, that is the probability of receiving ASA therapy, was calculated from a multiple logistic regression model. Covariates that were missing in a substantial portion of the study population were not included in the model (ethnicity, obesity, alcohol abuse, smoking status). Data were not available for many potential indications for ASA administration (coronary artery disease, cerebrovascular disease, peripheral vascular disease, hypertension). To address this limitation and to improve the performance of the propensity model, we included therapies often prescribed for these specific diagnoses (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers – ACE-I/ARB, statins, amiodarone). The variables included in the propensity model were age; gender; diabetes mellitus; cirrhosis; chronic kidney disease, stage V; congestive heart failure, New York Heart Association class IV; chronic obstructive lung disease; gastroesophageal reflux disease; immunosuppression; pre-hospitalization administration of ACE-I/ARB, statins, and/or amiodarone; and admission source. To further test the hypothesis that ASA was protective for the development of ALI, the Cochran-Mantel-Haenszel estimate of the pooled odds ratio was determined after stratifying the ASA propensity scores into equally-sized deciles. This approach allowed full use of the data and also provided stratum-by-stratum estimates of the ASA odds ratio to better understand the association with ALI.

Importantly, the empirical distributions of propensity scores were inherently different between the ASA treated and non-treated patients. To address this issue more fully, a sensitivity analysis was performed matching ASA-exposed patients to non-exposed patients, based on propensity score. A 0.1 caliper of propensity was used when identifying each ASA-exposed patient's non-exposed control(s). When possible, two non-exposed patients were matched to each ASA-exposed study participant. When a second non-exposed match could not be identified, a single ASA non-exposed match was accepted for the analysis. If no match could be identified for an ASA-exposed patient, the patient was excluded from the analysis. Conditional logistic regression was used to estimate the ASA treatment effect while conditioning on each matched set of case and control(s) (stratum).

All statistical analyses were performed using JMP statistical software base version 8.0 and SAS 9.1.4 (SAS Institute Inc., Cary, NC).

Results

A total of 3,855 patients met the inclusion and exclusion criteria and were included in this investigation. The flow of patient evaluation, exclusion, and enrollment are shown in Figure 1. A total of 976 (25.3%) were receiving ASA at the time of hospitalization. Demographic and baseline information are presented in Table 1. Patients taking ASA were older, more frequently Caucasian, and resided in a nursing home with greater frequency than non-ASA users. ASA users were more severely ill (higher APACHE II) at the time of hospital admission, but had similar estimated risk for developing ALI (similar LIPS). The ASA cohort had a greater frequency of pneumonia as the major risk for ALI while the non-ASA cohort had a higher frequency of lung contusion as a major risk factor. Differences in ALI risk modifiers between ASA users and non-users can be seen in Table 1. Specifically, ASA users had more prevalent diabetes mellitus, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and gastroesophageal reflux disease while the non-ASA group had a greater frequency of cirrhosis. ASA users were also more frequently obese and more frequently receiving ACE-I/ARB and statin therapy. In contrast, non-ASA users were more frequently receiving amiodarone and immunosuppressive therapy. Alcohol and tobacco use were also more prevalent in the non-ASA cohort.

A total of 240 (6.2%) patients developed ALI during their hospitalization with 159 meeting criteria for ARDS. The median time from hospital admission to AECC criteria for ALI/ARDS was 2 days (IQR: 2 to 5). Thirty-six patients developed ALI more than 7 days after hospital admission. Four of these were in the ASA cohort. Univariate analyses evaluating patient outcome by the presence of ASA therapy are shown in Table 2. Patients receiving ASA had a lower incidence of ALI (4.5% vs. 6.8%; odds ratio = 0.65; 95% CI = 0.46 to 0.90; $p = 0.010$) when compared to those not receiving ASA therapy. Statistical significance remained (odds ratio = 0.65; 95% CI = 0.43 to 0.98; $p = 0.036$) with the sensitivity analysis restricting the outcome to patients who developed ARDS (excluding patients only meeting criteria for ALI, $n = 81$). No statistically significant differences were noted in ICU or hospital mortality, nor ICU or hospital lengths of stay (Table 2).

A total of 3,814 patients were assigned a propensity score. Forty-one (1%) were not assigned a score due to missing data. The covariates included in the propensity model are shown in Table 3 and the results of the adjusted analyses stratifying patients by decile of propensity score are shown in Table 4. In the first strata, no patient receiving pre-hospitalization ASA therapy developed ALI. Therefore, an odds ratio for ASA could not be determined in this stratum. Overall, some heterogeneity in within-strata odds ratios was noted with estimates ranging from 0.26 (95% CI = 0.08 – 0.81) to 2.55 (95% CI = 0.29 – 22.09). Seven of the 9 strata with calculable odds ratios had point estimates for the odds ratio less than 1.0 (supportive of the hypothesis that ASA may have a protective effect for the development of ALI). The observed degree of heterogeneity did not lead to rejection of the null hypothesis of homogeneity required to compute the pooled estimate of the odds ratio (Breslow-Day p -value = 0.27). Accordingly, the pooled odds ratio as determined by the Cochran-Mantel-Haenszel test was calculated to be 0.70 (95% CI = 0.48 – 1.03; $p = 0.072$).

Sensitivity Analyses

The propensity score adjustment removed most of the potential confounding associated with baseline differences in ASA users and those not treated with ASA (propensity score adjusted p -values, Table 1). After adjusting by propensity score decile, only age, APACHE II score, use of statins, and lung contusion remained statistically different between the groups. Age, APACHE II score and statin use were all positively correlated, whereas the occurrence of lung contusion was negatively associated with this set of characteristics. To investigate if the residual differences in group characteristics affected the estimation of the ASA main effect, additional conditional logistic regression models were specified. Given the inter-correlation of the four variables, sensitivity models that modeled the ASA indicator along with each individual variable were considered (note: propensity score decile was still used as the stratification variable in the conditional logistic regression models).

The four sensitivity models that adjusted for propensity score decile and the residual potential confounding variable yielded similar results to the primary analysis with one exception. Adjustment for age, lung contusion or statin use yielded adjusted odds ratios (95% confidence intervals, p -values) of 0.70 (0.47 to 1.02, $p=0.064$); 0.72 (0.49 to 1.06, $p=0.092$) and 0.70 (0.48 to 1.03, $p=0.074$), respectively. Adjustment for APACHE II score produced a more profound effect on the estimated benefit of treatment with ASA. Specifically, the APACHE II score attenuated the estimated odds ratio from 0.70 to 0.81 (0.55 to 1.20, $p=0.30$), a 15% change in the effect estimate.

A second approach to the sensitivity analyses was developed that directly matched ASA users to non-users based on caliper matching of the propensity score. The conditional logistic regression evaluation of the association between ASA and development of ALI/ARDS, matching ASA-exposed patients to non-exposed patients by propensity score, was performed as outlined above. A total of 815 ASA-exposed were matched to 1221 non-

exposed patients (409 ASA-exposed had a single non-exposed match while 406 had two matches). There were 144 ASA-exposed patients for whom no match could be found. These individual's propensity scores averaged 0.71, with a minimum value of 0.51 and a maximum value of 0.91. An additional 1634 non-exposed subjects were unmatched and therefore not included in this sensitivity analysis. The remaining number (%) of ALI cases was 34 (4.17%) in the ASA-exposed cohort and 78 (6.39%) in the non-exposed group. In the conditional logistic regression analysis, the association between ASA treatment and ALI did not meet statistical significance (OR = 0.67; 95% CI = 0.44 – 1.01; $p = 0.055$).

Importantly, the short interval between hospital admission and development of ALI [median 2 days (IQR: 2 – 5 days)] raises the possibility that some patients may have been progressing to the full phenotype of ALI at the time of hospital admission (prevalent ALI) rather than having experienced incident ALI. In this circumstance, ASA may not be an effective therapeutic agent. To address this potential bias, we performed a sensitivity analysis evaluating the association between ASA therapy and ALI in the subgroup of patients who developed lung injury more than 2 days after hospital admission ($n = 129$). When adjusting for the propensity to receive ASA therapy, modeled as a covariate in a logistic regression model, the association between ASA and development of ALI was non-significant (adjusted odds ratio = 0.84; 95% CI = 0.50 – 1.38; $p = 0.13$). A final sensitivity analysis was performed to further detail the association between ASA therapy and development of more severe lung injury (ARDS cases only; ALI cases excluded), adjusting for the ASA propensity score modeled as a covariate in a logistic regression model. The effect estimate for this analysis was consistent with the primary analysis with an adjusted odds ratio (95% confidence interval) of 0.71 (0.44 – 1.11).

Discussion

In this investigation, we aimed to better define the association between pre-hospitalization ASA therapy and ALI/ARDS. To this end, initial univariate analyses supported the hypothesis of a protective effect with ASA therapy in patients at risk of ALI. However, inherent differences in the patients who received ASA, when compared to those who did not, limit the interpretation of this finding. To address this concern, propensity to receive ASA was incorporated into the analysis. Though the magnitude of the estimated effect remained clinically relevant and consistent with the unadjusted analyses, statistical significance was no longer present. No association between pre-hospitalization ASA therapy and ICU or hospital mortality, nor ICU or hospital lengths of stay was observed.

ALI is a multifactorial disease where immune cell migration and activation within the lung ultimately results in injury to the alveolar-capillary membrane (14, 41, 42). Mechanistically, endothelial injury/activation is known to result in platelet activation with resultant secretion of platelet granule contents, changes in platelet shape, and up-regulated expression of adhesion molecules such as P-selectin (13, 43). This process has been shown to result in enhanced thromboxane A₂ production (44), platelet aggregation (44), and secondary leukocyte capture (44, 45), leading to the full phenotype of ALI.

The key role of platelets in the pathogenesis of lung injury presents an opportunity for modulation with anti-platelet therapies such as ASA. In support of this hypothesis, blockade of P-selectin has been shown to reduce neutrophil recruitment and to have a protective effect in acid-induced ALI (44). Additionally, Looney et al. recently evaluated ASA's potential for lung protection in a two-hit animal model of transfusion-related acute lung injury (TRALI) (15). When compared to untreated animals, mice that received ASA prior to insult had marked reductions in plasma thromboxane B₂ production, lower extravascular lung water values and improved survival. Preclinical data suggests ASA may also enhance the

resolution of ALI by promoting the generation of anti-inflammatory lipids such as lipoxin A₄ (LXA₄) and 15-epi-LXA₄ (16, 17, 46). A growing body of clinical evidence suggests the potential to reduce organ dysfunction with ASA as well. Administration of anti-platelet therapy prior to hospital admission has recently been associated with improved organ function and reduced mortality in patients requiring intensive care unit support (47). More recently, our group confirmed the potential for ASA to prevent and/or attenuate ALI in a population-based cohort study of intensive care unit patients at high-risk of ALI (23).

Multiple potentially important factors may have contributed to our inability to reject the null hypothesis (no association between ASA therapy and incident ALI). First, the present investigation included multiple institutions (academic and community-based) with no standardized care processes between centers. The lack of standardization likely resulted in variable application of potentially important ALI-related health care delivery factors such as medication administration, nutritional support, conservative transfusion practices and fluid strategies, aspiration precautions, and ventilator management. Heterogeneity in the application of important care processes is expected to increase the variability of the effect estimate of interest (odds ratio for ALI in ASA and non-ASA users). The resultant widening of the effect estimate confidence intervals may contribute to the lack of statistical significance noted in our adjusted analyses. The study population of the present investigation is also more heterogeneous than that of our recent single-center investigation (23). The diverse study population may have compromised the internal validity of this study. In addition, the limited number of ALI outcomes in many of the strata included in the Cochran-Mantel-Haenszel test may have contributed to the loss of statistical significance in this analysis. Similarly, the reduction in sample size during the matching process may have also contributed to the loss of statistical significance in the conditional logistic regression analysis as well.

Alternatively, the lack of statistical significance in the present investigation may simply suggest that the association of ASA with attenuation of ALI is not as robust as previously believed. If true, several potential explanations exist. First, platelet activation may not be as central to ALI pathogenesis as previously believed. However, the growing body of literature supporting a central role for platelet activation in the pathogenesis of lung injury would argue against this possibility (13–18). Secondly, ASA may not effectively attenuate platelet activation in patients at risk for ALI. More specifically, the dose of ASA administered in this study may not have been sufficient to suppress platelet activation. ASA dose was not recorded at the time of the initial data extraction and the multicenter international nature of this investigation made post hoc ascertainment of ASA dose unfeasible. Although we are not able to comment on differential effects of the commonly administered ASA doses of 81 mg versus 325 mg, we do note that low dose ASA (81 mg daily) has been shown to effectively inhibit platelet thromboxane production and elevate plasma levels of LXA₄ with minimal additional effect at higher doses (48, 49). Differential effects on the attenuation of lung injury may occur with alternative anti-platelet therapies as well. These data were not collected for this investigation and we cannot comment further on this possibility.

While the large sample size, prospective multi-center design, and well-defined variable criteria with explicit standard operating procedures are strengths of the present investigation, several limitations deserve note. First, the observational nature of this study creates potential for confounding and bias. Although efforts were made to control for these issues during development of the study design, data collection, and statistical analysis, potential for unmeasured confounding effects remains. The observational study design also precludes the standardization of other important care processes which could confound the association of interest. An additional limitation is the lack of information regarding ASA dose and medication administration following hospital admission. The extended duration of ASA's

effect on platelet function and the short interval from hospital admission to ALI onset (median 2 days [IQR: 2 – 5 days]) attenuates the potential significance of ASA discontinuation following hospital admission. Finally, our inclusion criteria mandated admission to the hospital. Therefore, our findings may not generalize well to at-risk patients who are not admitted to the hospital.

Conclusions

In summary, after adjusting for the propensity to receive ASA therapy, we did not identify a statistically significant association between ASA administration and incident ALI. However, the results observed in this study do align qualitatively with a growing body of pre-clinical data and a recent single-center observational study suggesting lung protection with ASA. The inability to completely remove the effects of confounding from this observational study, coupled with the growing body of literature detailing ASA's efficacy in this setting, supports clinical equipoise and the importance of a randomized clinical trial evaluating ASA's potential for lung protection

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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USCIITG LIPS1 participating centers and corresponding investigators

Mayo Clinic Rochester, Minnesota: Adil Ahmed, MD; Ognjen Gajic, MD; Michael Malinchoc, MS; Daryl J Kor, MD; Bekele Afessa, MD; Rodrigo Cartin-Ceba, MD; Rickey E Carter, PhD; Departments of Internal Medicine, Health Sciences Research and Anesthesiology

University of Missouri, Columbia: University of Missouri-Columbia: Ousama Dabbagh, MD, MSPH, Associate Professor of clinical medicine; Nivedita Nagam, MD; Shilpa Patel, MD; Ammar Kar; and Brian Hess

University of Michigan, Ann Arbor: Pauline K. Park, MD, FACS, FCCS, Co-Director, Surgical Intensive Care Unit, Associate Professor, Surgery; Julie Harris, Clinical Research Coordinator; Lena Napolitano, MD; Krishnan Raghavendran, MBBS; Robert C. Hyzy, MD; James Blum, MD; Christy Dean

University of Texas Southwestern Medical Center in Dallas, Texas: Adebola Adesanya, MD; Srikanth Hosur, MD; Victor Enoch, MD; Department of Anesthesiology, Division of Critical Care Medicine

University of Medicine and Dentistry of New Jersey: Steven Y. Chang, PhD, MD, Assistant Professor, MICU Director, Pulmonary and Critical Care Medicine; Ameer Patrawalla, MD, MPH; Marie Elie, MD

Brigham and Women's Hospital: Peter C. Hou, MD; Jonathan M. Barry, BA; Ian Shempp, BS; Atul Malhotra, MD; Gyorgy Frendl, MD, PhD; Departments of Emergency Medicine, Surgery, Internal Medicine and Anesthesiology Perioperative and Pain Medicine, Division of Burn, Trauma, and Surgical Critical Care

Wright State University Boonshoft School of Medicine & Miami Valley Hospital: Harry Anderson, III MD, Professor of Surgery; Kathryn Tchorz, MD, Associate Professor of Surgery; Mary C. McCarthy, MD, Professor of Surgery; David Uddin, PhD, DABCC, CIP, Director of Research

Wake Forest University Health Sciences, Winston-Salem, NC: J. Jason Hoth, MD, Assistant Professor of Surgery; Barbara Yoza, PhD, Study Coordinator

University of Pennsylvania: Mark Mikkelsen, MD, MSCE, Assistant Professor of Medicine, Pulmonary, Allergy and Critical Care Division; Jason D. Christie, MD; David F. Gaieski, MD; Paul Lanken, MD; Nuala Meyer, MD; Chirag Shah, MD

Temple University School of Medicine: Nina T. Gentile, MD, Associate Professor and Director, Clinical Research, Department of Emergency Medicine, Temple University School of Medicine; Karen Stevenson, MD, Resident, Department of Emergency Medicine; Brent Freeman, BS, Research Coordinator; Sujatha Srinivasan, MD, Resident, Department of Emergency Medicine

Mount Sinai School of Medicine: Michelle Ng Gong, MD, MS, Assistant Professor, Pulmonary, Critical Care and Sleep Medicine, Department of Medicine

Beth Israel Deaconess Medical Center, Boston, Massachusetts: Daniel Talmor, MD, Director of Anesthesia and Critical Care, Associate Professor of Anaesthesia, Harvard Medical School; S. Patrick Bender, MD; Mauricio Garcia, MD

Massachusetts General Hospital Harvard Medical School: Ednan Bajwa, MD, MPH, Instructor in Medicine; Atul Malhotra, MD, Assistant Professor; B. Taylor Thompson, Associate Professor; David C. Christiani, MD, MPH, Professor

University of Washington, Harborview: Timothy R. Watkins, MD, Acting Instructor, Department of Medicine, Division of Pulmonary and Critical Care Medicine; Steven Deem, MD; Miriam Treggiari, MD, MPH

Mayo Clinic Jacksonville: Emir Festic, MD; Augustine Lee, MD; John Daniels, MD

Akdeniz University, Antalya, Turkey: Melike Cengiz, MD, PhD; Murat Yilmaz, MD

Uludag University, Bursa, Turkey: Remzi Iscimen, MD

Bridgeport Hospital, Yale New Haven Health: David Kaufman, MD, Section Chief, Pulmonary, Critical Care & Sleep Medicine, Medical Director, Respiratory Therapy

Emory University: Annette Esper, MD; Greg Martin, MD

University of Illinois at Chicago: Ruxana Sadikot, MD, MRCP

University of Colorado: Ivor Douglas, MD

Johns Hopkins University: Jonathan Sevransky, MD, MHS, Assistant Professor of Medicine, Medical Director, JHBMC MICU

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References

1. Jepsen S, Herlevsen P, Knudsen P. Antioxidant treatment with n-acetylcysteine during adult respiratory distress syndrome: a prospective randomized placebo controlled study. *Crit Care Med*. 1992; 20(7):918–923. [PubMed: 1617983]
2. Thompson BT. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA*. 2000; 283(15):1995–2002. [PubMed: 10789668]
3. Wiedemann HP, Arroliga AC, Komara J, et al. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Critical Care Med*. 2002; 30(1):1–6. [PubMed: 11902249]
4. Meade MO, Jacka MJ, Cook DJ, et al. Survey of interventions for the prevention and treatment of acute respiratory distress syndrome. *Critical Care Med*. 2004; 32(4):946–954. [PubMed: 15071383]
5. Zeiher BG, Artigas A, Vincent J-L, et al. Neutrophil elastase inhibition in acute lung injury: Results of the STRIVE study. *Critical Care Med*. 2004; 32(8):1695–1702. [PubMed: 15286546]
6. Gajic O, Frutos-Vivar F, Esteban A, et al. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med*. 2005; 31(7):922–926. [PubMed: 15856172]
7. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Critical Care Med*. 2004; 32(9):1817–1824. [PubMed: 15343007]
8. Yilmaz M, Keegan MT, Iscimen R, et al. Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med*. 2007; 35:1660–1666. [PubMed: 17507824]
9. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest*. 2007; 131(5):1308–1314. [PubMed: 17400669]
10. Gajic O, Rana R, Winters JL, et al. Transfusion Related Acute Lung Injury in the Critically Ill: Prospective Nested Case-Control Study. *Am J Respir Crit Care Med*. 2007; 176(9):886–891. [PubMed: 17626910]
11. Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995; 151(2 Pt 1):293–301. [PubMed: 7842182]
12. Mojarad M, Hamasaki Y, Said SI. Platelet-activating factor increases pulmonary microvascular permeability and induces pulmonary edema. A preliminary report. *Bull Eur Physiopathol Respir*. 1983; 19(3):253–256. [PubMed: 6882949]
13. Zarbock A, Ley K. The role of platelets in acute lung injury (ALI). *Front Biosci*. 2009; 14:150–158. [PubMed: 19273059]
14. Zarbock A, Polanowska-Grabowska RK, Ley K. Platelet-neutrophil-interactions: linking hemostasis and inflammation. *Blood Rev*. 2007; 21(2):99–111. [PubMed: 16987572]
15. Looney MR, Nguyen JX, Hu Y, et al. Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. *J Clin Invest*. 2009; 119(11):3450–3461. [PubMed: 19809160]
16. El Kebir D, Jozsef L, Pan W, et al. 15-epi-lipoxin A4 inhibits myeloperoxidase signaling and enhances resolution of acute lung injury. *Am J Respir Crit Care Med*. 2009; 180(4):311–319. [PubMed: 19483113]
17. Fukunaga K, Kohli P, Bonnans C, et al. Cyclooxygenase 2 Plays a Pivotal Role in the Resolution of Acute Lung Injury. *J Immunol*. 2005; 174(8):5033–5039. [PubMed: 15814734]
18. Maderna P, Godson C. Lipoxins: resolutionary road. *Br J Pharmacol*. 2009; 158(4):947–959. [PubMed: 19785661]
19. Chelucci GL, Boncinelli S, Marsili M, et al. Aspirin effect on early and late changes in acute lung injury in sheep. *Intensive Care Med*. 1993; 19(1):13–21. [PubMed: 8440792]
20. Sigurdsson GH, Vallgren S, Christenson JT. Influence of aspirin and steroids on acute lung injury after i.v. injection of a sclerosing agent. *Acta Chir Scand*. 1989; 155(3):163–170. [PubMed: 2741624]

21. Yasuda O, Takemura Y, Kawamoto H, et al. Aspirin: recent developments. *Cell Mol Life Sci.* 2008; 65(3):354–358. [PubMed: 18038215]
22. Jin SW, Zhang L, Lian QQ, et al. Posttreatment with aspirin-triggered lipoxin A4 analog attenuates lipopolysaccharide-induced acute lung injury in mice: the role of heme oxygenase-1. *Anesth Analg.* 2007; 104(2):369–377. [PubMed: 17242094]
23. Erlich JM, Talmor DS, Cartin-Ceba R, et al. Pre-hospitalization anti-platelet therapy is associated with a reduced incidence of acute lung injury: A population-based cohort study. *Chest.* 2011; 139(2):289–295. [PubMed: 20688925]
24. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007; 147:573–577. [PubMed: 17938396]
25. Gajic O, Dabbagh O, Park PK, et al. Early Identification of Patients at Risk of Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a Multicenter Cohort Study. *Am J Respir Crit Care Med.* 2010 Aug 27. (epub ahead of print).
26. Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005; 33(6): 1191–1198. [PubMed: 15942330]
27. Derdak S. Acute respiratory distress syndrome in trauma patients. *J Trauma.* 2007; 62(6 Suppl):S58. [PubMed: 17556976]
28. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med.* 2001; 344(9):665–671. [PubMed: 11228282]
29. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. *Crit Care.* 2007; 11(5):R96. [PubMed: 17784960]
30. Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27–28 April 2006; *Intensive Care Med*; 2007. p. 575-590.
31. Matthay MA, Zimmerman GA, Esmon C, et al. Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. *Am J Respir Crit Care Med.* 2003; 167(7):1027–1035. [PubMed: 12663342]
32. Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA.* 1996;50–54. [PubMed: 8531287]
33. Fernandez-Perez ER, Sprung J, Afessa B, et al. Intraoperative ventilator settings and acute lung injury after elective surgery: A nested case-control study. *Thorax.* 2009; 64(2):121–127. [PubMed: 18988659]
34. Gong MN, Bajwa EK, Thompson BT, et al. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax.* 2010; 65(1):44–50. [PubMed: 19770169]
35. Mangialardi RJ, Martin GS, Bernard GR, et al. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. *Ibuprofen in Sepsis Study Group. Crit Care Med.* 2000; 28(9):3137–3145. [PubMed: 11008971]
36. Iscimen R, Cartin-Ceba R, Yilmaz M, et al. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. *Crit Care Med.* 2008; 36(5):1518–1522. [PubMed: 18434908]
37. Naito Y, Tsuchiya S, Ishihara S, et al. Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. *Am J Clin Oncol.* 2008; 31(4):340–344. [PubMed: 18845992]
38. Levitt JE, Bedi H, Calfee CS, et al. Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest.* 2009; 135(4):936–943. [PubMed: 19188549]
39. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. *Crit Care Med.* 2000; 28(7):2187–2192. [PubMed: 10921539]
40. Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination; *Am J Respir Crit Care Med*; 1994. p. 818-824.

41. Kodama T, Yukioka H, Kato T, et al. Neutrophil elastase as a predicting factor for development of acute lung injury. *Intern Med*. 2007; 46(11):699–704. [PubMed: 17541219]
42. Perl M, Lomas-Neira J, Chung CS, et al. Epithelial cell apoptosis and neutrophil recruitment in acute lung injury - a unifying hypothesis? What we have learned from small interfering RNAs. *Mol Med*. 2008; 14(7–8):465–475. [PubMed: 18368145]
43. Tabuchi A, Kuebler WM. Endothelium-platelet interactions in inflammatory lung disease. *Vascular Pharmacology*. 2008; 49(4–6):141–150. [PubMed: 18625343]
44. Zarbock A, Singbartl K, Ley K. Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. *J Clin Invest*. 2006; 116(12):3211–3219. [PubMed: 17143330]
45. Schulz C, Schafer A, Stolla M, et al. Chemokine fractalkine mediates leukocyte recruitment to inflammatory endothelial cells in flowing whole blood: a critical role for P-selectin expressed on activated platelets. *Circulation*. 2007; 116(7):764–773. [PubMed: 17679613]
46. Morris T, Stables M, Hobbs A, et al. Effects of low-dose aspirin on acute inflammatory responses in humans. *J Immunol*. 2009; 183(3):2089–2096. [PubMed: 19597002]
47. Winning J, Neumann J, Kohl M, et al. Antiplatelet drugs and outcome in mixed admissions to an intensive care unit. *Crit Care Med*. 2010; 38(1):32–37. [PubMed: 19770746]
48. Chiang N, Bermudez EA, Ridker PM, et al. Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. *Proc Natl Acad Sci USA*. 2004; 101:15178–15183.
49. Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005; 353:2373–2383. [PubMed: 16319386]

Figure 1.
Study participant flow chart.

Table 1

Demographics and baseline characteristics.

Parameter	ASA (n = 976)	No ASA (n = 2879)	Raw p-value	Propensity Score Adjusted p-value ^c
Age ^a	70 (59 – 81)	51 (38 – 66)	< 0.001	0.037
Gender (Female) ^b	435 (44.6)	1305 (45.3)	0.681	0.882
Caucasian (n = 3747) ^b	659 (69.2)	1695 (60.7)	< 0.001	0.178
Admission Source ^b			< 0.001	0.984
Home	683 (71.2)	2254 (79.0)	--	--
Nursing Facility	134 (14.0)	194 (6.8)	--	--
Outside ED	102 (10.6)	286 (10.0)	--	--
Other	40 (4.2)	121 (4.2)	--	--
APACHE II ^a	12 (8 – 16)	9 (5 – 14)	< 0.001	0.002
LIPS score ^a	2.5 (1.5 – 4.0)	2.5 (1.5 – 4.0)	0.311	0.115
ALI Predisposing Conditions				
Aspiration ^b	52 (5.3)	151 (5.2)	0.920	0.608
Pneumonia ^b	391 (40.1)	834 (29.0)	< 0.001	0.312
Pancreatitis ^b	68 (7.0)	240 (8.3)	0.173	0.120
Sepsis ^b	443 (45.4)	1306 (45.4)	0.989	0.377
Shock ^b	91 (9.3)	274 (9.5)	0.858	0.061
High risk trauma ^b				
Traumatic brain injury	91 (9.3)	356 (12.4)	0.010	0.109
Smoke inhalation	4 (0.4)	21 (0.7)	0.282	0.741
Near drowning	1 (0.1)	1 (0.03)	0.442	0.068
Lung Contusion	9 (0.9)	157 (5.5)	< 0.001	0.006
Multiple fractures	65 (6.7)	233 (8.1)	0.147	0.225
ALI risk modifiers				
Diabetes Mellitus ^b	393 (40.3)	576 (20.0)	< 0.001	0.996
Cirrhosis ^b	18 (1.8)	90 (3.1)	0.036	0.753
CKD, Stage V ^b	79 (8.1)	108 (3.8)	< 0.001	0.815
CHF, NYHA class IV ^b	79 (8.1)	58 (2.0)	< 0.001	0.227
COPD ^b	178 (18.2)	281 (9.8)	< 0.001	0.882
Interstitial lung disease ^b	13 (1.3)	30 (1.0)	0.456	0.625
Gastroesophageal reflux ^b	171 (17.5)	283 (9.8)	< 0.001	0.897
BMI (n = 3096) ^a	26.7 (22.9 – 31.6)	26.0 (22.3 – 30.7)	0.004	0.136
Obesity (BMI > 30) ^b	256 (31.9)	635 (27.7)	0.023	0.131
ACE-inhibitors/ARB's ^b	434 (44.5)	483 (16.8)	< 0.001	0.492

Parameter	ASA (n = 976)	No ASA (n = 2879)	Raw p-value	Propensity Score Adjusted p-value ^c
Statins ^b	530 (54.3)	405 (14.1)	< 0.001	0.018
Amiodarone ^b	18 (0.6)	17 (1.7)	0.002	0.934
Smoking (n = 3565) ^b			< 0.001	0.623
Never	456 (50.0)	1356 (51.1)	--	--
Former	296 (32.5)	518 (19.5)	--	--
Active	160 (17.5)	779 (29.4)	--	--
Alcohol use (n = 3447) ^b	222 (25.0)	895 (35.0)	< 0.001	0.629
Albumin (n = 1772) ^a	3.5 (2.9 – 3.9)	3.5 (2.9 – 4.0)	0.500	0.303
Chemotherapy ^b	36 (3.7)	115 (4.0)	0.670	0.668
Immunosuppression ^b	86 (8.8)	353 (12.3)	0.003	0.618
Hematocrit (n = 3721) ^a	35.1 (31.0 – 39.5)	36.2 (31.6 – 40.7)	< 0.001	0.717
Platelet count (n = 3704) ^a	229 (169 – 306)	232 (172 – 303)	0.806	0.543

ICU = intensive care unit, APACHE = acute physiology and chronic health evaluation, LIPS = lung injury prediction score, RR = respiratory rate, CAD = coronary artery disease, CVD = cerebrovascular disease, CHF = congestive heart failure, BMI = body mass index, FiO₂/PaO₂ = fraction of inspired oxygen to partial pressure of arterial oxygen ratio, DNR = do not resuscitate, DNI = do not intubate.

^a median with interquartile range,

^b counts (%),

^c P-value obtained for each characteristic predicting ASA administration from a conditional logistic regression model that stratified by propensity score deciles.

Table 2

Univariate analysis of patient outcome by the presence or absence of aspirin administration.

Outcome	Aspirin (n = 976)	No aspirin (n = 2879)	p-value
ALI ^a	44 (4.5)	196 (6.8)	0.010
ICU Mortality ^a	39 (4.0)	134 (4.7)	0.391
Hospital Mortality ^a	63 (6.5)	180 (6.3)	0.822
ICU length of stay ^b	2 (0 – 5)	2 (0 – 5)	0.132
Hospital length of stay ^b	5 (4 – 9)	5 (3 – 10)	0.930

ALI = acute lung injury, ICU = intensive care unit.

^a counts (%),

^b median with 25% – 75% interquartile range.

Table 3

Nominal logistic regression model for development of the aspirin propensity score.

Covariate	Odds Ratio	95% CI	p-value
Age ^a	1.04	1.04 – 1.05	< 0.001
Sex (male)	1.23	1.03 – 1.46	0.020
Admission Source ^b			
Nursing Home	1.13	0.85 – 1.49	0.388
Referring Emergency Department	1.13	0.85 – 1.50	0.386
Other	1.14	0.73 – 1.74	0.563
Diabetes Mellitus	1.38	1.14 – 1.67	< 0.001
Cirrhosis	0.92	0.51 – 1.58	0.785
Chronic Kidney Disease, Stage V	1.82	1.27 – 2.59	0.001
Congestive Heart Failure, Class IV	2.30	1.54 – 3.44	< 0.001
Chronic Obstructive Pulmonary Disease	1.18	0.93 – 1.49	0.181
Gastroesophageal Reflux Disease	1.45	1.14 – 1.85	0.003
Immunosuppression	0.97	0.73 – 1.29	0.843
ACE-I/ARB	1.98	1.64 – 2.39	< 0.001
Statin	3.63	3.02 – 4.38	< 0.001
Amiodarone	1.30	0.61 – 2.74	0.495

CI = confidence interval; ACE-I/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

^a per year increase in age.

^b odds of receiving ASA therapy versus the odds of receiving ASA therapy among those admitted from home.

Table 4

Adjusted analyses evaluating the association between pre-hospitalization aspirin therapy and development of acute lung injury after stratifying by decile of aspirin propensity.

Strata	Propensity Score Range ^a	Proportion develop ALI on Aspirin	Proportion develop ALI without Aspirin	Odds Ratio	95% CI	p-value
1 (n = 380)	0.019 to 0.035	0/3 (0%)	20/377 (5.0%)	n/a	n/a	--
2 (n = 382)	0.035 to 0.055	1/7 (14.3%)	23/375 (6.1%)	2.55	0.29 – 22.09	--
3 (n = 382)	0.055 to 0.080	1/16 (6.3%)	34/366 (9.3%)	0.65	0.08 – 5.08	--
4 (n = 381)	0.080 to 0.110	1/27 (3.7%)	26/354 (7.3%)	0.49	0.06 – 3.72	--
5 (n = 382)	0.111 to 0.159	2/56 (3.6%)	29/326 (8.9%)	0.38	0.09 – 1.64	--
6 (n = 382)	0.159 to 0.241	6/103 (5.8%)	18/279 (6.5%)	0.90	0.35 – 2.33	--
7 (n = 381)	0.241 to 0.333	4/122 (3.3%)	17/259 (6.6%)	0.48	0.16 – 1.47	--
8 (n = 381)	0.334 to 0.464	10/163 (6.1%)	7/218 (3.2%)	1.97	0.73 – 5.29	--
9 (n = 382)	0.464 to 0.627	4/211 (1.9%)	12/171 (7.0%)	0.26	0.08 – 0.81	--
10 (n = 381)	0.628 to 0.955	15/251 (6.0%)	9/130 (6.9%)	0.85	0.36 – 2.01	--
Overall (n = 3814) ^b	--	--	--	0.70	0.48 – 1.03	0.072

ALI = acute lung injury; CI = confidence interval.

^aBoundaries appear disjointed due to rounding

^bOverall (pooled) estimate of the odds ratio estimated by Mantel-Haenszel stratified estimator. For stratum 1, the standard odds ratio was not calculable due to the zero cases of ALI in the aspirin treated patients. The “empirical” odds ratio, which adds 0.5 to all cells in the stratum 1 contingency table yields a pooled estimate of the odds ratio of 0.77 (0.51 to 1.14). The Breslow-Day test for homogeneity of the odds ratios had a p-value of 0.27, a value supporting the pooling of odds ratios across strata.