AHC Media

Vol. 21, Issue 2, May 2013
www.ahcmedia.com

Critical Care [ALERT]

A monthly update of developments in critical care and intensive care medicine

SPECIAL FEATURE

Lung Recruitment Maneuvers in Acute Respiratory Distress Syndrome

By Richard H. Kallet, MS, RRT, FAARC, FCCM
Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital
Mr. Kallet reports no financial relationships relevant to this field of study.

A recruitment maneuver (RM) is the technique of briefly increasing alveolar pressure to levels in excess of what normally is recommended to reopen collapsed peripheral airways and alveoli so that both resting lung volume, or functional residual capacity (FRC), and oxygenation are restored.[1] Moreover, amelioration of sheer injury through reversal of atelectasis is a major component in preventing ventilator-induced lung injury (VILI) in patients with acute respiratory distress syndrome (ARDS). This special feature will provide a brief overview of the physiologic foundation and history of RMs as well as discuss its clinical application.

PHYSICS AND PHYSIOLOGY OF THE RECRUITMENT MANEUVER

The RM is inextricably related to the pulmonary pressure volume (compliance) curve and the concept of hysteresis. Moving the lungs from a relatively collapsed to a fully inflated state produces a leftward shift in the pressure-volume relationship (that is, improved compliance).[1] During subsequent deflation to FRC, tidal ventilation requires a lower driving pressure that lessens the risk for VILI. In essence, the RM is the same phenomenon that occurs with the first postnatal breath. At birth, the initial recruitment of the gasless lung requires a critical opening pressure of -40 cm H_2O to begin inflation and pressures approaching -80 cm H_2O to achieve full inflation.[2] Similarly, inflation of a collapsed, excised lung (at residual volume) requires a lower critical opening pressure of 20 cm H_2O; thereafter, recruitment proceeds unevenly until full inflation is achieved at a transpulmonary pressure of 40 cm H_2O.[2]

Financial Disclosure: *Critical Care Alert*'s editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, peer reviewer William Thompson, MD, executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Critical Care [ALERT]

Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Critical Care Alert, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $349
Add $17.95 for shipping & handling. (Student/Resident rate: $120).

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 1-9 additional copies: $215 each; 10 or more copies: $191 each.

Back issues: $40 Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add GST and $30 shipping. Elsewhere: Add $30 shipping.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, 30304 and at additional mailing offices.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity has been approved for 13.3 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider #14749, for 13.3 Contact Hours. This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

Reversal of significant lung collapse not only requires high inflation pressures, but those pressures must also be sustained for a period of time. This temporal component is particularly important in ARDS. Lung recruitment is determined by numerous factors, including the surface tension, viscosity and film thickness of the airway lining fluid, airway radius, axial wall traction exerted by the surrounding alveoli, and the presence of surfactant.[3] Increased lining fluid surface tension raises the applied airway pressure necessary to reopen collapsed airways, while an increased viscosity (as with protein-rich pulmonary edema fluid) prolongs the time necessary to reopen sequentially collapsed airways.[3] The opening pressure must also counter the superimposed weight of the edematous lung itself, the mediastinum and chest wall, as well as disperse edema fluid and cellular debris residing in the small airways and alveoli.[1]

BRIEF HISTORY

In the early 1960s, the term "pulmonary hyperinflation" was used to describe the reopening of collapsed air spaces to reverse intraoperative atelectasis and hypoxemia.[4] This was achieved with sustained (15 seconds) inflation pressures of 30-40 cm H_2O. The term "recruitment" was introduced in the 1970s to describe how positive end-expiratory pressure (PEEP) improved pulmonary function.[5,6] The fact that recruitment occurred because the concomitant increase in inspiratory pressure at a constant tidal volume (Vt) exceeded the critical opening pressure was only alluded to and not emphasized. It was only in 1992 with the advocacy for "open-lung ventilation" that the concepts of recruitment/derecruitment and the attendant roles of inspiratory plateau (i.e., alveolar) pressure (Pplat) and PEEP were clearly delineated.[7] By the end of the 1990s, publications focusing on RMs began to appear regularly in the medical literature, such that now several hundred publications on the topic are listed in Pubmed.

METHODOLOGY

Two common methods for lung recruitment are 1) applying continuous positive airway pressures (CPAP) of 35-40 cm H_2O for 40 seconds[8] and 2) a "maximum recruitment" strategy of stepwise super-PEEP using pressure control ventilation. In this approach, an initial PEEP of 25 cm H_2O is set with a driving pressure of 15 cm H_2O to achieve a Pplat of 40 cm H_2O for 4 minutes.[9] Typically, a low respiratory frequency and prolonged inspiratory time (e.g., 10 and 3 seconds, respectively) are set to enhance recruitment. If cardiorespiratory stability is maintained, then PEEP is titrated upwards in 5 cm H_2O increments at the same driving pressure for 2 minutes. Then the ventilator is returned to the initial RM settings for evaluation either by arterial blood gases or pulse oximetry. Full recruitment has been defined as the achievement of a $PaO_2 + PaCO_2 \geq 400$ mmHg (using an FIO_2 of 1.0). If pulse oximetry is used, then the FIO_2 is titrated to achieve an SpO_2 of 90-92% so that improvements or deteriorations in oxygenation are readily apparent. If recruitment goals are not met, then the RM is repeated at the next highest pressure increment. The maximum RM settings with this technique are a PEEP of 45 cm H_2O and a Pplat of 60 cm H_2O.

Both the maximum recruitment and high CPAP methods incorporate a decremental PEEP trial following the RM because many studies found that the positive effects of an RM dissipate within a few minutes to hours.[1] In the decremental PEEP method, optimal PEEP is determined empirically by a quick (e.g., 5-20 minutes) stepwise PEEP reduction of 2 cm H_2O until a mild deterioration in either oxygenation or compliance is detected.[10] This signifies the beginning of derecruitment and the RM then is repeated. Afterwards, PEEP is set 2 cm H_2O above the level at which derecruitment was detected. This procedure can be streamlined as several studies have shown that measuring pulmonary dead-space fraction is a more sensitive indicator of derecruitment that occurs prior to deterioration in oxygenation.[11]

Of note, in a heterogeneously injured

lung, delayed or progressive derecruitment often occurs whereby oxygenation and compliance deteriorate over a matter of hours, not minutes. This may be more prevalent when chest wall compliance is low and a constant external force acts to compress the lungs. Therefore, clinicians should anticipate that determining "optimal PEEP" by the decremental PEEP method may be biased toward underestimating the actual PEEP requirements post RM.

IN WHOM, WHEN, AND HOW?

While clearly beneficial in restoring lung volume and improving gas exchange, RMs create radical changes in intrathoracic pressures and volumes that can result in hemodynamic instability, cardiac arrhythmias, acute hypoxemia, and pulmonary barotrauma.[1] In a recent study of 366 patients receiving up to four RMs daily using the CPAP method, 22% experienced complications, and the latter were significantly related to the number of RMs attempted and to the patients' having a "direct" or pulmonary form of ARDS (e.g., pneumonia, aspiration, pulmonary contusion).[12] The most common problems were transient hypotention (11%), oxygen desaturation (10%), and tachycardia/bradycardia (5%). Both arrhymias and barotrauma were rare (1% each). Moreover, there is no high-level evidence that incorporation of RMs improves clinically significant outcomes in ARDS so that the risk/benefit ratio of RMs may seem unattractive.

Patient selection and timing of the RM are also important factors as RMs are not effective in all patients with ARDS. The best indicator for using an RM is the same as that for escalating PEEP therapy: patients with low FRC tend to have the greatest potential for lung recruitment.[6] FRC essentially represents the alveolar volume and is a major determinant of both compliance and PaO_2. Although the potential for lung recruitment varies widely in ARDS, patients with poorer oxygenation, lower compliance, and higher dead-space fraction tend to exhibit a higher degree of lung recruitment.[13] RMs tend to be more effective if instituted during the early (exudative) phase of the syndrome.[1]

However, this is not always true, and a recent study of patients with early ARDS and relatively profound hypoxemia reported that only half of them responded positively to a maximum recruitment strategy.[14] As in other studies, non-responders tended to be those with direct lung injury, which classically is associated with both consolidation and limited recruitable lung tissue. Responders tended to have "non-pulmonary" etiologies of ARDS (e.g., sepsis, pancreatitis). And yet, even these general tendencies do not always hold true. Others have found that some patients with direct pulmonary injury do respond positively to RMs.[10] Therefore, clinicians ultimately must evaluate RMs in individual patients empirically and not be overly swayed by tendencies reported in the literature as it currently exists.

But the most important unaddressed issue pertains to the temporal aspects of lung recruitment. It is clear that in the absence of elevated PEEP, the benefits of RMs are ephemeral. Therefore, could similar improvements in pulmonary gas exchange and mechanics be achieved if higher PEEP levels simply were used for longer durations? The fear of high PEEP partly reflects the findings of studies establishing PEEP's adverse effects back in the early 1970s. These were done with large Vts (often 15-20 mL/kg) that contributed significantly to the incidence of hypotension and barotrauma. For example, even at modest levels of PEEP, Vts between 10-20 mL/kg caused abrupt deterioration in compliance. Yet in these same patients, compliance continued to improve when physiologic Vts were used (5-7 mL/kg), even at 15 cm H_2O of PEEP.[15]

Recent studies suggest that lower levels of super-PEEP (i.e., 20-25 cm H_2O) with physiologic Vts appear to be well tolerated.[9,10] Over an extended period of time, such an approach might be sufficiently effective as an RM and may carry less risk of adverse effects. Incorporating prone positioning may further enhance lung recruitment by favorably altering the dorsal-ventral pleural pressure gradient while preventing overdistension of the non-dependent lung.[16]

In the context of severe ARDS, the risk/benefit ratio of using RMs as an adjunctive therapy appears reasonable. However, appropriate patient selection, meticulous evaluation, preparation, and monitoring are key to maximizing the benefits of RMs while minimizing adverse effects (*see Table*).

Assuring normovolemia and correction of hypotension are essential. Keeping in mind that the RM reduces/redistributes pulmonary perfusion, hypotension will obscure the detection of alveolar recruitment. In these situations, titrating vasopressor support to achieve and maintain a mean arterial pressure of at least 70 mmHg is useful in facilitating real-time evaluation of lung recruitment. In situations where hypotension is refractory to therapy, then the RM should only be attempted using intermittent sighs on the ventilator. Some ventilators do this with an "intermittent PEEP" function, whereby PEEP

Table. A Practical Guide for Considering Recruitment Maneuvers in ARDS

Indications	Contraindications
1. Diffuse opacities and/or low lung volumes on chest radiograph	1. Untreated pneumothorax
2. Extra-pulmonary source of ARDS (e.g., sepsis, pancreatitis, nonthoracic trauma)	2. Presence of subcutaneous, mediastinal, or pericardial air
3. Low lung compliance (e.g., ≤ 35 mL/cm H_2O)	3. Severe obstructive lung disease
4. Superimposed lobar collapse	4. Radiologic evidence of hyperinflation
5. Inability to maintain stable oxygenation (PaO_2 ≥ 65 mm Hg) on both moderately high PEEP (e.g., ≥ 15 cm H_2O) and FIO_2 ≥ 0.70 that limits the ability to carry out routine patient care or other necessary procedures without severe oxygen desaturation	5. Unilateral lung disease
	6. Infections known to weaken lung architecture (e.g., necrotizing pneumonia, *Pneumocystis jiroveci* pneumonia)
	7. Mean arterial pressure < 60 mmHg
	8. Intracranial hypertension
	9. Severe cor pulmonale

is raised transiently to a clinician-selected level for two breaths every few minutes. This method has been shown to improve oxygenation and lung volumes.[17] However, this approach may be less effective than common RM methods.

In patients with severe acidosis and hypermetabolism, it is probably better to choose the maximum recruitment method as even relatively brief periods of apnea can increase the risk of instability. Careful analysis of minute ventilation demand, $PaCO_2$, and pH prior to the RM is useful in setting the baseline minute ventilation during the RM and to evaluate the potential need for buffer therapy. THAM (tris buffer) is particularly useful in this regard, as it does not produce CO_2 and has been used to achieve apneic oxygenation.[18] Finally, assuring passive ventilation with a neuromuscular blocking agent is important to prevent active expiratory efforts that promote derecruitment and reduce the risk of barotrauma.

SUMMARY

RMs are beneficial in restoring lung volume and improving gas exchange in patients with ARDS, but as yet no evidence exists to suggest that they improve outcomes. Adverse effects are relatively frequent but usually are transient and resolve with termination of the procedure. When its use is restricted to the early phase of severe ARDS, particularly in those with an "extra-pulmonary etiology," RMs tend to be more effective in stabilizing pulmonary function and reasonably justify potential risks. Several methods of RMs are available and should be chosen after careful evaluation of individual patients. ■

REFERENCES

1. Kacmarek RM, Kallet RH. *Respir Care* 2007;52:622-631.
2. Cherniack RM, et al. *Respiration in Health and Disease*. 2nd ed. Philadelphia: WB Saunders; 1972.
3. Gaver DP, et al. *J Appl Physiol* 1990;69:74-85.
4. Bendixen HH, et al. *N Engl J Med* 1963;269:991-996.
5. Falke KJ, et al. *J Clin Invest* 1972;51:2315-2323.
6. Suter PM, et al. *N Engl J Med* 1975;292:284-289.
7. Lachmann B. *Intensive Care Med* 1992;18:319-321.
8. Amato MBP, et al. *N Engl J Med* 1998;338:347-354.
9. Borges JB, et al. *Am J Respir Crit Care Med* 2006;174:268-278.
10. Tugrul S, et al. *Crit Care Med* 2003;31:738-744.
11. Kallet RH. *Minerva Anesthesiol* 2012;78:1297-1305.
12. Fan E, et al. *Respir Care* 2012;57:1842-1849.
13. Gattinoni L, et al. *N Engl J Med* 2006;354:1775-1786.
14. Moran I, et al. *Minerva Anesthesiol* 2011;77:1167-1175.
15. Suter PM. *Chest* 1978; 73:158-162.
16. Cornejo RA, et al. *Am J Respir Crit Care Med* 2013; Jan. 24. [Epub ahead of print.]
17. Foti G, et al. *Intensive Care Med* 2000;26:501-507.
18. Nahas GG, et al. *Drugs* 1998;55:191-224.

ABSTRACT & COMMENTARY

Can Chest CT Help Predict Quality of Life in Acute Lung Injury Survivors?

By Betty Tran, MD, MS

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

Dr. Tran reports no financial relationships relevant to this field of study.

SYNOPSIS: This study reports a correlation between the degree of abnormalities on high-resolution chest CT and both restrictive pulmonary dysfunction and poorer health-related quality of life among survivors of acute lung injury.

SOURCE: Burnham EL, et al. Chest computed tomography features are associated with poorer quality of life in acute lung injury survivors. *Crit Care Med* 2013;41:445-456.

This collaborative study using data from a randomized controlled trial of acute lung injury (ALI) sought to determine whether pulmonary dysfunction contributed to poorer quality of life among survivors of ALI at 6 months and whether abnormalities on chest high-resolution CT (HRCT) were associated with and could predict its development.

The authors included 89 patients with ALI who had 180-day pulmonary function testing (PFT) and day 14 and/or day 180 chest HRCTs performed. They specifically excluded patients with a known history of underlying chronic obstructive pulmonary disease and interstitial lung disease. A radiologic score was developed to quantify the extent of a radiographic pattern (ground-glass opacification, intense parenchymal opacification, and reticulation) seen throughout the lungs. Higher chest HRCT scores indicated more radiographic involvement by a given pattern. Quality-of-life outcomes were measured at 180 days using the short form (SF)-36 and St. George's respiratory questionnaires (SGRQ).

Of the 47 patients who had day 180 PFTs and chest HRCTs, overall HRCT scores were associated with decreased total lung capacity ([TLC] r = -0.60, P = 0.003). Higher day 180 HRCT scores were associated with poorer SF-36 physical function, role physical, and physical health subtotal scores (r = -0.4, P = 0.01 for all comparisons) and poorer SGRQ activity, impact, and total scores (r = 0.5-0.6, $P < 0.05$ for all comparisons). Both lower PFT parameters and higher HRCT scores at 180 days were associated with some pulmonary factors such as higher average plateau pressure exposure and a diagnosis of pneumonia as a risk factor for ALI. In multivariable models, forced vital capacity (FVC) was the only variable associated with poorer SF-36 physical health subtotal and SGRQ total scores; there was a trend of higher day 180 chest HRCT scores correlating with poorer SGRQ total scores, but this was not statistically significant.

Data from 43 patients who had chest HRCTs at day 14 revealed that higher HRCT scores were associated with lower TLC (r = -0.60, P = 0.0001), poorer SF-36 physical function, role physical, and physical health subtotal scores (r = -0.4 to -0.5, $P < 0.05$ for all comparisons), and poorer SGRQ activity, impacts, and total scores (r = 0.5-0.6, $P < 0.05$ for all comparisons). Higher day 14 HRCT scores were associated with fewer ventilator, ICU, and hospital-free days. In multivariable analyses, day 14 chest HRCT scores remained independently associated with lower SF-36 and poorer SGRQ scores measured at day 180.

COMMENTARY

The authors attempt to address whether the poorer quality of life and functional impairment seen in survivors of ALI can be attributable to pulmonary dysfunction rather than neuromuscular weakness, the latter of which has been and continues to be extensively studied. Results of the current study, however, are unable to make this distinction definitively. Only a modest number of ALI patients were included from the parent trial, and it is not surprising that the presence of day 180 HRCT abnormalities correlated with abnormal PFTs performed at the same time. However, the data examining the association between day 180 HRCT scores and poorer quality of life are limited by the fact that most chest HRCTs had normalized over the 6-month follow-up period, with wide variability in quality of life among those who had, on average, low HRCT scores. As a result, the regression lines used to model the association between day 180 chest HRCT scores and SF-36 and SGRQ scores appear to be overly influenced by a few data points, representing the very small number of patients

who had more abnormal HRCTs 6 months after ALI diagnosis. Furthermore, the observation that day 180 FVC was the only variable significantly associated with poorer quality of life rather than HRCT scores in multivariable analyses suggests that nonpulmonary factors (e.g., neuromuscular weakness) may be playing a larger role.

Significant associations between day 14 chest HRCT scores with lung function and quality of life 6 months later were observed, although it is difficult to attribute these outcomes causatively to pulmonary dysfunction. It is conceivable that patients with more abnormal CTs 2 weeks into their ALI course were sicker (as evidenced by fewer ventilator, ICU, and hospital-free days in this group) and subsequently had longer rehabilitation times, higher rates of neuromuscular weakness, and poorer quality of life. The lack of formal nerve conduction/electromyographic testing for any of the patients was a significant limiting factor in eliminating neuromuscular dysfunction as a potential contributor to the observed associations. Overall, although this study was limited in its ability to delineate between pulmonary and neuromuscular etiologies for abnormal PFTs and poor quality of life among ALI survivors, the question is an important one to address as the answer could result in different therapeutic options that are offered. ■

ABSTRACT & COMMENTARY

Are Long-Term Acute Care Hospitals Cost Effective for Chronically Critically Ill Patients?

By Linda L. Chlan, RN, PhD

Dean's Distinguished Professor of Symptom Management Research, The Ohio State University, College of Nursing

Dr. Chlan reports that she receives grant/research support from the National Institutes of Health.

SYNOPSIS: Chronically critically ill patients who receive care in either acute care ICUs or in long-term acute care hospitals have similar 1-year survival rates. However, long-term acute care hospitals incur a higher overall cost, due to higher Medicare reimbursement rates to these facilities.

SOURCE: Kahn JM, et al. Effectiveness of long-term acute care hospitalization in elderly patients with chronic illness. *Medical Care* 2013;51:4-10.

The authors of this large, retrospective cohort study compared survival and health care utilization costs in patients > age 65 who transferred to a long-term acute care (LTAC) hospital with those factors in patients who remained in an acute care hospital's ICU. Data were abstracted and linked from several large national databases for the years 2002-2006. These included the Medicare Provider Analysis and Review (MedPAR) Files, the Medicare Denominator File, zip code-level population data from the U.S. census, and year-specific hospital characteristics from the Center for Medicare and Medicaid Healthcare Cost Report Information System (HCRIS). The investigators pointed out that Medicare is the primary payer for 75% of LTAC patients. The primary outcome was survival within 1 year. Secondary outcomes were three types of costs and spending for: 1) the entire episode of acute care and LTAC hospitalization, 2) post-acute care hospitalization, and 3) 180-day hospitalization-related costs including the initial acute care stay and the post-acute care period. A series of regression models, including proportional hazards regression and linear regression, were applied to the large dataset considering covariates of age, gender, race, socio-economic status, comorbidities, and hospital status (for profit, nonprofit, government).

A total of 234,799 patients were considered in the final sample, with 20.6% of these patients transferred to LTACs. A majority of the LTACs (71.7%) were for profit, followed by nonprofit (22.5%) and government owned (5.8%); half were co-located in an acute care facility and half were free standing. Clinical and demographic characteristics were similar between the two patient groups, including 1-year mortality. Transfer to an LTAC was associated with lower total and post-acute care costs, but with higher Medicare payments. The main driver of lower costs for LTAC patients was the reduction in post-acute care hospitalizations. The investigators concluded that initial lower costs for patients transferred to LTACs are primarily based on earlier transfer out of the ICU and a reduction in admissions for skilled nursing facilities, as these types of care settings are a main contributor to health care costs in this patient population post-ICU.

COMMENTARY

The investigators note in their article that LTACs were among the fastest growing segment of acute care in the United States until 2007 when a moratorium was placed on the certification of new facilities. This may have been due in part to growth in Medicare spending and reimbursement for LTACs. While these facilities provide care for a small but resource-intensive group of patients, in general this group of chronically critically ill patients have poor outcomes. Thus, the investigators were interested in comparing survival and health care costs for Medicare beneficiaries in LTACs vs those who remain in acute care ICUs. Surely, acute care ICUs are more expensive to provide care for these high-resource intensive patients. Surprisingly, the results of this large cohort study that used sophisticated econometric principles did not support this supposition. While LTACs indeed are specialized care centers for the chronically critically ill, the study from Kahn and colleagues indicates these facilities may be more expensive in the long run due to higher Medicare reimbursement rates.

On some levels, the results of this cohort study highlight everything that is wrong with the U.S. health care system. The United States spends more on health care than any other industrialized nation, yet we do not have superior outcomes. In this study, the survival was the same for patients transferred to LTACs as for those patients who remained hospitalized with chronic critical illness in acute care ICUs. This does not seem possible that similar outcomes were achieved, yet at a much higher cost due to reimbursement rates!

While the principle behind LTACs is sound, an examination of how they are reimbursed is needed. Kahn et al are to be commended for shedding some light on the reimbursement issue and raising awareness that there is no difference in outcomes related to survival in patients transferred to LTACs compared to those who remain in acute care ICUs. The investigators recommend some sort of bundled payments for care and the implementation of accountable care organizations to rein in costs for these complex patients, with the inclusion of their findings to begin to inform policy on payment models for acute care and LTACs. ■

ABSTRACT & COMMENTARY

Is Your Smart Phone Spreading Infection in the ICU?

By David J. Pierson, MD, Editor

SYNOPSIS: Bacteria were present on the cell phones of all hospital clinicians studied, with potentially pathogenic microorganisms isolated from 29% of them. Contamination with pathogens was found more commonly with smart phones than with non-smart phones, and by multivariable analysis no other factor was associated with this difference.

SOURCE: Lee YJ, et al. Contamination rates between smart cell phones and non-smart cell phones of healthcare workers. *J Hosp Med* 2013;8:144-147.

Lee and colleagues administered questionnaires and performed bacterial cultures on the cellular phones of 203 clinicians (39% physicians, 52% nurses, 9% medical assistants) working in three university-affiliated teaching hospitals in Seoul. The questionnaire included data on participant demographics (age, gender, occupation) as well as behavior regarding cell phone use (type of cell phone, frequency and reasons for use, and cleaning of cell phones). The investigators touched the anterior and posterior surfaces of the phones onto blood agar plates and classified the recovered bacteria according to pathologic potential. Among probable pathogenic microorganisms, representative drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, and imipenem-resistant *Acinetobacter baumannii* were categorized as drug-resistant pathogens. The participants' mean age was 29 years and 79% were women. A total of 115 (57%) were smart phone users and 88 (43%) used non-smart phones. The smart phone users were slightly younger (28 vs 29 years, $P = 0.03$), but this was the only significant difference between the groups. Only a minority of all cell phone users reported taking special measures to clean them.

All 203 cell phones had positive cultures: 4% had a single organism recovered, 19% had two organisms, and 76% had three or more. The most

commonly cultured microorganism was coagulase-negative staphylococci, isolated from 96% of the phones. Gram-positive bacilli and *Micrococcus* species were also frequently recovered. Probable pathogenic bacteria were isolated from 58 cell phones (29%). *S. aureus* was the most common of these, and it was MRSA in 8 of the 50 instances. *Acinetobacter baumannii* was recovered from five phones. Probable pathogens were isolated more often from smart phones (35% vs 20% of non-smart phones, $P = 0.03$). The total colony count of probable pathogens from smart phones was also higher (average, 5.5 vs 5.0 from non-smart phones, $P = 0.01$). Among all the factors examined for possible association with phone contamination, only the phone's being a smart phone was found to be a risk factor for contamination by bacteria with pathogenic potential (adjusted odds ratio [OR] 4.02; 95% confidence interval [CI], 1.43-11.31; $P = 0.01$). Using the cell phone more than 10 times during working hours appeared to be associated with pathogen contamination; however, this correlation failed to reach statistical significance (OR, 2.9; 95% CI, 0.9-9.3; $P = 0.07$).

■ COMMENTARY

This study found that health care workers' smart phones were more frequently contaminated with potentially pathogenic bacteria than non-smart phones. The authors postulate two reasons for this — that smart phones have larger surfaces that are more often touched by the user's fingers, and that they may be used more times during the day, since clinicians can use them for more work-related tasks than non-smart phones.

Other studies have documented frequent bacterial contamination of the cell phones of health care workers — along with their stethoscopes and various parts of their attire — as well as of the bed rails, monitors, bedside curtains, computer keypads, and other features of the patient's immediate environment. Direct linkage between such contamination and specific cases of hospital-acquired infection has generally been lacking, although it is hard to ignore the possibility of this or measures aimed at avoiding it. Cell phones are now carried by virtually all health care workers. Today, more and more of these are smart phones, which are increasingly being integrated into clinical and administrative aspects of critical care. How concerned we should be about their contamination with potential pathogens is not entirely certain, but we should be aware of the fact that such organisms are present not only on our hands but also on the things we carry around with us in the ICU. ■

CME/CNE Questions

1. The purported benefits of a recruitment maneuver include all of the following *except*:

a. improvement in functional residual capacity.
b. reduced need for PEEP.
c. improvement in lung compliance.
d. reduced atelectasis.
e. increased oxygenation.

2. In acute lung injury survivors at 180 days, patients who had high resolution chest CTs which showed more abnormalities were more likely to have:

a. lower total lung capacity.
b. poorer physical functioning.
c. poorer scores on St. George's respiratory questionnaire.
d. a history of exposure to higher plateau pressures while on the ventilator.
e. All of the above

3. Which of the following statements is true regarding costs associated with long-term acute care hospitals (LTACs)?

a. An average of five new LTACs/year are financed each year by the federal government.
b. LTACs are cost effective due to a lower rate of Medicare reimbursement than acute care facilities.
c. LTACs are more expensive due to a higher rate of Medicare reimbursement.
d. LTACs are cost neutral due to the pay-for-service model.
e. None of the above

4. Which of the following factors was associated with a higher risk for cell phone contamination with potentially pathogenic bacteria?

a. The fact that the user was a physician vs a nurse or other worker
b. Female gender
c. The user's having recently cared for a patient with methicillin-resistant *S. aureus*
d. The fact that the cell phone was a smart phone
e. All of the above

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Volume 18, Number 5 | Pages 9-10 | May 2013

Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■