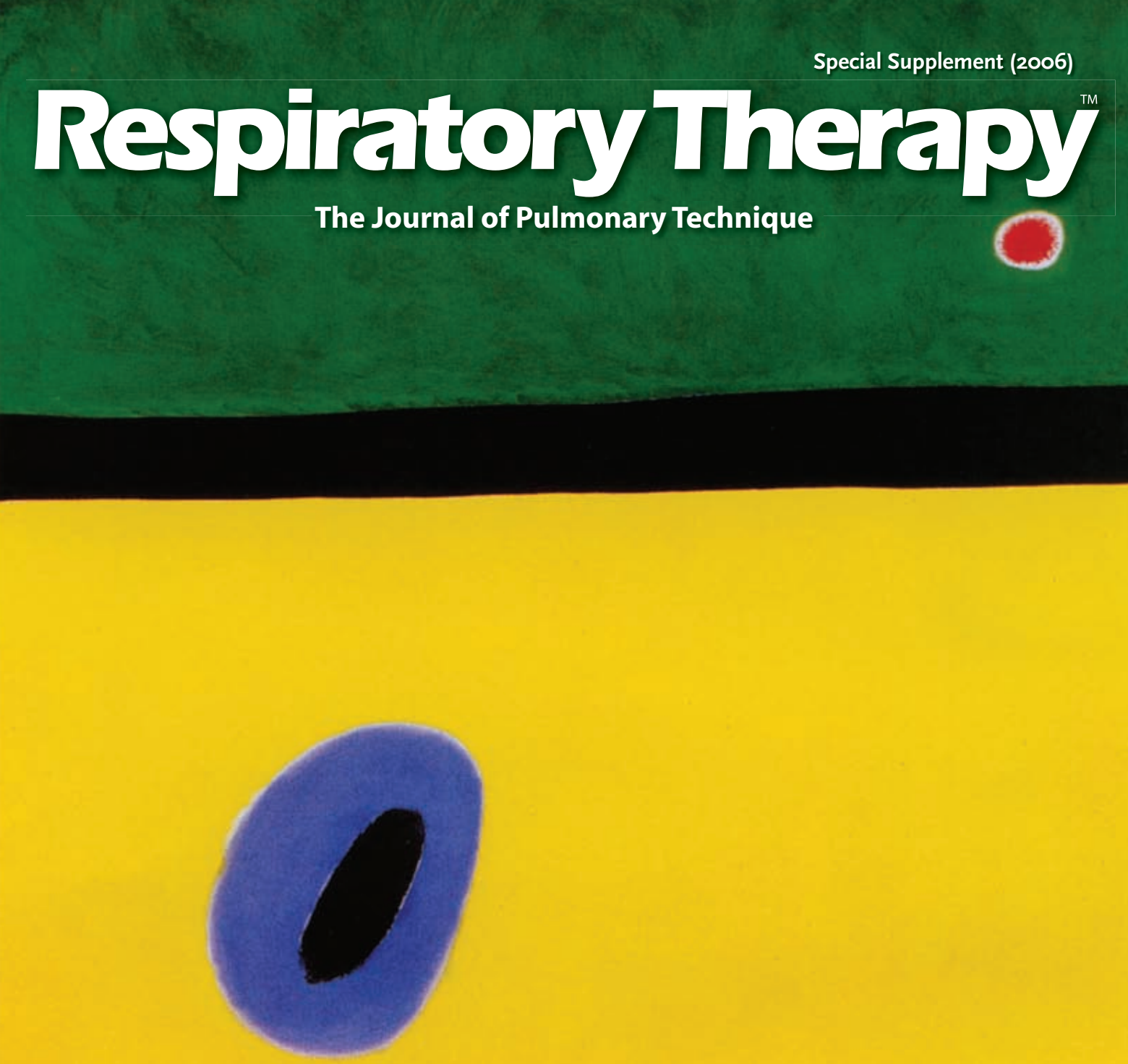
Special Supplement (2006)

# Respiratory Therapy™

The Journal of Pulmonary Technique



## DRIVING STANDARDS OF CARE WITH pH PLEURAL FLUIDS, BILIRUBIN RESULTS IN THE NICU, AND ACID-BASE MAPPING

# Editorial

## FILLING A NEED

Clinicians and the companies that serve them are always searching for new ways to improve blood gas analysis, searching for better, more efficient ways to ensure accuracy of measurement and timeliness of providing vital test information. To meet this need, we have assembled a compendium of valuable information about the latest advances in blood gas by Roche Diagnostics. In this special supplement, we look state-of-the-art approaches to testing for bilirubinemia and pH on pleural fluid. Why are these important?

The National Vital Statistics Report estimates an annual caseload of more than 80,000 newborns with bilirubin levels in excess of 20 mg/dL. Elevated bilirubin levels such as these have been linked to kernicterus.

Advances in laboratory medicine are often driven by the need to obtain more information from a smaller sample at a faster time than previously possible. Precise and accurate determination of plasma total concentrations is indispensable for proper management of jaundiced infants. Especially for monitoring hyperbilirubinemia, direct photometry of neonatal whole-blood samples in a blood gas analyzer provides fast yet reliable results from very small sample volumes, enabling bilirubin measurement at the point of care.

Why is there a need for more vital information? A recent study noted, "pediatricians are aware of the message regarding the importance of preventing severe hyperbilirubinemia and hyperbilirubinemia-related neurological complications. However, pediatricians' uncertainties about the utilization of diagnostic approaches and risk factor identification, and their significant tendency for lower utilization of bilirubin levels post-discharge for the initiation of phototherapy, suggests the need for greater education in order to promote evidence-based practices for the prevention and management of neonatal hyperbilirubinemia and kernicterus."

Pleural fluid pH testing can facilitate early diagnosis and intervention, which can help eliminate costly and unnecessary treatments. pH pleural fluid testing provides the physician with a valuable diagnostic test that complements the clinical decisions necessary to provide excellence in patient outcomes.

Another need for accurate and fast laboratory data occurs when clinicians request pH on pleural fluid. Still today, most pH testing on pleural fluids is performed on pH meters of litmus paper. Due to the nature of the method, the sample must be exposed to the air and this can alter the result. Minor changes in pH can change the clinician's interpretation.

By measuring pH pleural fluids on a blood gas analyzer, accuracy and speed to result are enhanced. Additionally, the use of a blood gas analyzer for pleural fluid pH measurement is consistent with recommendations by both the American College of Chest Physicians and the College of American Pathologists.

Here's what you'll find in this report on recent advances by Roche Diagnostics:

- LUNG INFECTION AND PUBLIC HEALTH
- PLEURAL FLUID pH OVERVIEW
- PLEURAL FLUID pH ANALYSIS IN THE BLOOD GAS LAB
- WHY USE A BLOOD GAS SYSTEM WITH FDA 510(k) CLEARANCE FOR PLEURAL FLUID pH TESTING?
- BILIRUBIN DETERMINATION USING THE OMNI S POINT OF CARE ANALYZER
- ACCURACY OF NEAR-PATIENT TESTING OF BILIRUBIN AND HEMATOCRIT MEASUREMENT WITH THE OMNI S BLOOD GAS ANALYZER
- WHY IS A 1-MINUTE BILIRUBIN TEST ESPECIALLY IMPORTANT IN THE NICU?
- BLOOD GASES – A CLINICAL PRIMER
- HOW CAN AUTOMATED ACID-BASE MAPPING HELP YOU DELIVER A MORE PRECISE DIAGNOSIS AND THERAPY MONITORING?
- EXECUTIVE PROFILE: RODNEY COTTON, SENIOR VICE PRESIDENT, POINT OF CARE DIAGNOSTICS, DISCUSSES THE ROCHE OMNI S BLOOD GAS ANALYZER
- BLOOD GAS TECHNOLOGY: AN INTERVIEW WITH KEN LEVY, DIRECTOR OF HOSPITAL POINT OF CARE

The publisher and editors of Respiratory Therapy are proud to present this much needed and valuable compendium of information. For more on the above technologies and products, please contact Roche Diagnostics.

Les Plesko, Editor
Respiratory Therapy

While attending the AARC Congress in Las Vegas, come visit Roche Diagnostics at booth 603. For more information contact Mike Kolodkin, Manager of Marketing, Hospital Point of Care.

# Lung Infection-A Public Health Priority

Joseph P. Mizgerd

Emerging lung infections capture the world's imagination because of the potential for pandemics. Recent examples include avian influenza and the severe acute respiratory syndrome (SARS). However, even in the absence of new pathogens or pandemics, lung infections have tremendous impact. Lung infections cause more disease than better-recognized threats to the public's health such as cancer, heart attacks, strokes, HIV/AIDS, tuberculosis, or malaria. This persistent and pervasive burden of lung infections receives proportionately little attention from the biomedical and public health communities.

## THE GLOBAL BURDEN OF LUNG INFECTIONS

The Burden of Disease Project[1] at the World Health Organization (WHO) collects statistics that can be used to determine the public health impact of different diseases. The metric of disability-adjusted life years (DALYs) lost takes into account the amount of otherwise healthy life lost to morbidity and or/mortality. Diseases were categorized according to the International Classification of Diseases (ICD) from WHO.[2]

The "lung infections" category includes "Influenza and pneumonia" (ICD-10 codes J10-18) and "Other acute lower respiratory infections" (ICD-10 J20-22), but it excludes "Tuberculosis" (ICD-10 A15-19) and "HIV disease resulting in infectious and parasitic diseases" (ICD-10 B20). By excluding respiratory tuberculosis as well as pneumonias in patients with HIV/AIDS, these statistics might be considered by some to underestimate the burden of disease due to lung infections. Even with these exclusions, lung infections accounted for more than 6% of the total global burden of disease in 2002. This disease burden is greater than that of other better-recognized causes of disease (Figure 1). This impressive burden is not an anomaly of that particular year, due to SARS or any other unusual epidemic or event, but is instead the norm. Since 1990, when WHO began compiling and presenting such statistics, lung infections have consistently caused more burden than any of the diseases identified in Figure 1.[3, 4]

## THE DISPROPORTIONATE BURDEN ON THE POOR

Lung infections are especially common and severe among the poor. When the relative burden of disease in communities is assessed by normalizing DALYs to population size, lung infections caused the loss of 2,983 DALYs/100,000 population in the poorest regions compared to 137 DALYs/100,000 population in the wealthiest. Thus, poverty is associated with a more than 20-fold increase in the relative burden of lung infections.

According to WHO, 2.6 billion people live in "Low Income" countries, with Gross National Income (GNI) per capita ≤US$765, and 2.2 billion people live in "Lower Middle Income" countries, with GNI per capita of US$766-US$3,035. This single incremental improvement in income is associated with a dramatic difference in the relative burden of disease caused by lung infections. Lung infections caused the loss of 535 DALYs per 100,000 population in the "Lower Middle Income" population in 2002. Comparing this figure to the relevant figures listed above, it may be surmised that the vast majority (86%) of the difference due to income occurs between the lowest income group and the next-to-lowest income group. Thus, the poor are especially likely to suffer from lung infections, and relatively modest income improvements may substantially lessen their burden of lung infection. As with many infectious diseases,[5] fighting poverty and improving health care for the impoverished will greatly decrease the global burden of lung infections.

## LUNG INFECTIONS THREATEN ALL ECONOMIC GROUPS

Among those who live in wealthy societies, infectious diseases cause less of a burden than do chronic diseases such as cancers and cardiovascular diseases. However, even among advantaged populations, lung infections are remarkably prominent. In the wealthiest as well as the poorest regions of the world, lung infections cause a greater burden than any other infectious disease (Figure 2). Thus, while climbing the socioeconomic

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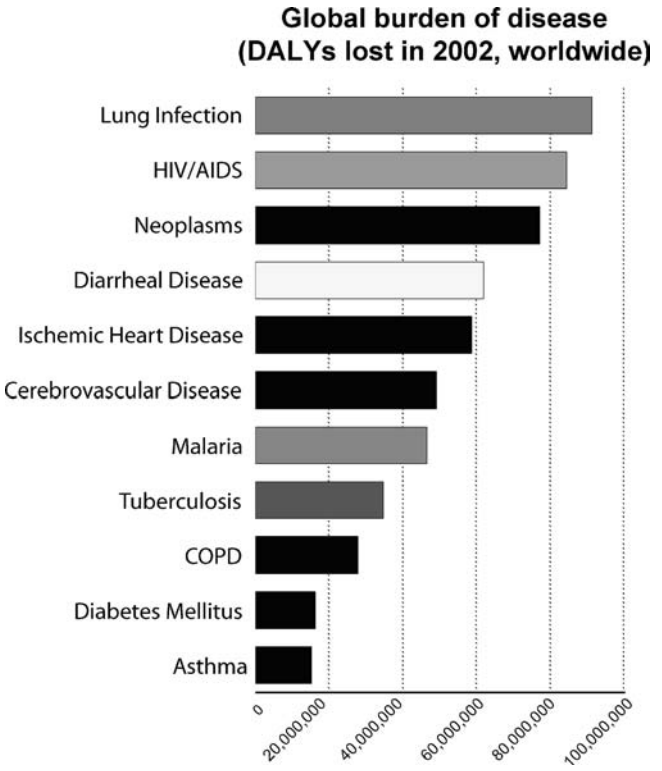


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**Figure 1.** The Global Burden of Selected Diseases in 2002, as Measured by Disability-Adjusted Life Years (DALYs) Lost Worldwide
COPD, chronic obstructive pulmonary disease

ladder associates with a lesser burden, lung infections threaten across the economic spectra.

For those in wealthier populations, little further advancement is evident against lung infections. Focusing exclusively on the highest income populations ("Established Market Economies" or "High Income" groups in the WHO Burden of Disease Study), a comparison of the relative DALY losses due to lung infection shows little change from 1990 to 2002 (151 and 137 DALYs lost/100,000 population, respectively), whereas there have been dramatic improvements in the burdens due to other diseases within these wealthy communities. For example, among the wealthiest populations, HIV in 2002 caused less than half the disease it did in 1990 (from 159 to 72 DALYs lost/100,000 population). There are no DALY statistics available prior to 1990, but other indicators such as the US mortality rate due to pneumonia and influenza suggest that, for wealthy countries, there has been little or no progress against lung infections since the first half of the last century.[6]

For several reasons, lung infections in wealthy countries seem poised to become even more of a concern in the near future. First, in these populations, advancing age makes lung infections increasingly more prevalent and life-threatening.[7] Therefore, demographic shifts resulting in an expanding elderly community in wealthy countries[8] suggest that more and more people are likely to suffer severely from lung infections. Second, novel respiratory infections emerge frequently, some of which can be highly virulent. Recent examples include SARS[9] and avian influenza.[10] If and when these new infections emerge, globalization increases the likelihood that such respiratory infections will become rapidly widespread.[11] Third, microbes that cause lung infections are increasingly resistant to previously effective antibiotics. While effective medical and public health practice will hopefully prevent the arrival of a "post-antibiotic" era,[12] the continuously diminishing number of drugs effective against Streptococcus pneumoniae, Pseudomonas aeruginosa, and other common agents of community and hospital-acquired pneumonias raises concern.

## EFFORTS AND RESOURCES

All diseases included in Figures 1 and 2, and many not listed, are critical targets of research and health care. All require more funding and more effort than they now receive. However, if some diseases (such as lung infections) are less widely recognized as critical threats to our health, then resources and efforts will be allocated suboptimally, resulting in poorly tailored responses to public health needs.

Determining whether funds are contributing to research against a given disease is horribly inexact. Furthermore, the conceptual advances with most promise against a particular disease may more likely result from basic research than from disease-focused research. However, substantial resources are allocated to understanding and fighting particular diseases, and biomedical progress against those diseases is influenced by these targeted efforts. While the greatest burdens of disease and the greatest threats to the public health might be presumed to receive the greatest shares of research funding, they do not.

The US National Institutes of Health (NIH) spent approximately US$28 billion on health-related research in 2004,[13] of which US$287 million was allocated to lung infections. This is substantive and laudable, but it must be considered in perspective. It pales in comparison with the US$1.63 billion spent on biodefense. More NIH money is spent on smallpox research (US$324 million) alone than on lung infection research. While it is essential to be proactive in recognizing, preventing, and preparing for looming or emerging threats to public health, it may be questioned whether funding for speculated risks should so overwhelm funding for diseases already causing such tremendous burdens.

Lung infection research is also poorly funded when compared with other currently significant public health concerns. For example, US$2.85 billion were spent on HIV/AIDS research, which is substantially improving prospects against this very important disease. It is remarkable, though, that lung infections cause a comparable or greater disease burden (Figures 1 and 2), yet they receive only one-tenth of HIV/AIDS research funding. In a similar vein, the NIH allocated comparable resources to lung infections as to sexually transmitted diseases (US$237 million), even though in wealthy countries such as the US lung infections cause seven times more disease than do sexually transmitted diseases (Figure 2), with even larger differentials in poorer countries. These figures from the NIH are but a few examples demonstrating that lung infections are relatively under-represented.

Reacting to the pandemic threat of the recently emerging avian influenza virus (H5N1), the president of the US recently requested a lump sum totaling US$7.1 billion.[14] The majority of requested funds in the president's plan, more than US$5.3 billion, would be slated for the manufacture, purchase, and stockpile of vaccines and antivirals targeting influenza. An additional US$0.8 billion would be allocated for research on

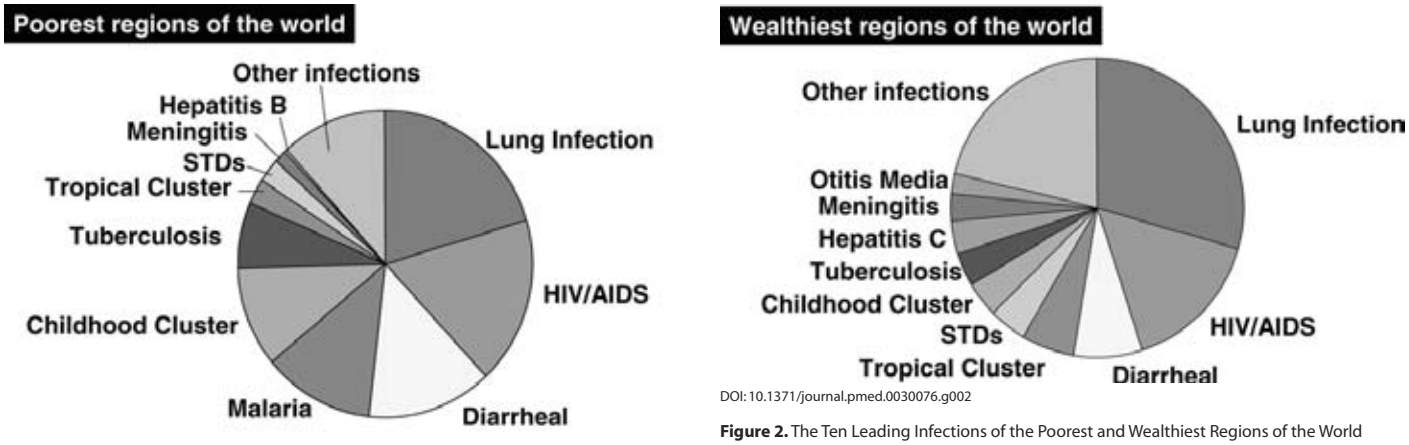


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**Figure 2.** The Ten Leading Infections of the Poorest and Wealthiest Regions of the World
These leading infections are represented as a fraction of the total infectious disease burden of that region, and are in clockwise descending order. (STDs, sexually transmitted deseases excluding HIV)

new vaccines and antivirals against influenza, US$0.6 billion for influenza preparedness planning, and US$0.3 billion to help countries detect and contain influenza outbreaks. It is this author's opinion that the immediate need for such immense resources results from the potential of a severe influenza pandemic combined with many years of inadequate attention to lung infections. As of the time of writing this essay, the US Congress has yet to approve funding, and it remains unclear how much will be approved and how it will be deployed if approved, but a discrete set of funds may soon become available for fighting influenza specifically.

It is more difficult to assess resources distributed by private organizations, but it is again evident that lung infections are underemphasized. US News and World Report identifies 20 charities as the largest to deal specifically with diseases and disease-related research.[15] Of these 20 leading charities, nine focus on cancer, two on organs (heart or kidney), two on classes of disease (mental illness or birth defects), and the rest on six specific diseases (muscular dystrophy, diabetes, multiple sclerosis, cystic fibrosis, Alzheimer disease, and arthritis). Perhaps the most prominent philanthropy focused specifically on infectious disease is The Global Fund to Fight AIDS, Tuberculosis, and Malaria.[16] This fund reports that it has attracted commitments of US$4.7 billion from national governments, private companies, and other contributors for fighting these three specific diseases. Such philanthropies perform wonderful services in improving health. Lung infections would similarly benefit from such a major philanthropic focus.

## INFECTIOUS DISEASE THROUGH THE PRISM OF MICROBIOLOGY

Why does the consistent burden of lung infections receive so little attention? It may result in part from our tendency to view infectious diseases from a microbiology perspective. Microbes can reasonably be portrayed and perceived as enemies to be attacked and defeated. Smallpox eradication is a powerful illustration of the potential of such an approach. Because AIDS is caused by HIV, malaria by Plasmodia, tuberculosis by Mycobacteria, and so on, defeating HIV and Plasmodia and Mycobacteria are widely recognized as valid goals in virtually any informed community.

While the idea of fighting against a specific microbe is attractive, and such an "us-against-them" mentality is effective at mobilizing commitments, a microbe-specific focus is appropriate for some infectious diseases more than others. Lung infections do not result from one or a few extremely virulent microbes especially adapted to living in our lungs. Rather, a tremendous variety of microbes causes lung infections, and a strategy focused on the microbes is destined to be a game of catch-up. The physiology of breathing requires our lungs to be enormously exposed to microbes, both from the external environment (the air) and from a microbe-rich part of our anatomy (our upper airways). It is inevitable that microbes land in our lungs. In part for these reasons, respiratory infections are common, and new respiratory pathogens are likely to emerge frequently. Eliminating microbes in the lungs requires inflammatory responses that by their very nature compromise ventilation and blood-gas exchange. Thus, eliminating infection threatens physiology, and in part for this reason respiratory infections are often severe.

Tools are available for targeting some microbes causing lung infections (e.g., vaccines and antibiotics). Further research into reactive strategies directed specifically against individual microbes will likely improve our abilities to prevent or cure select lung infections. Few and marginally effective tools are available for targeting exposures of host responses to lung infection (e.g., ultraviolet germicidal irradiation or corticosteroids, respectively). Forward-thinking strategies might be directed at determinants of respiratory tract exposure, innate immune defenses against microbes in the lungs, and inflammatory injury resulting from lung infection. Advances in these areas will provide opportunities both to combat ongoing public health crises and to limit the potential threat from emerging pathogens.

## CONCLUSION

Like the proverbial elephant in the room, lung infections are a persistent problem not receiving the attention required. This may result in part from the nature of a disease lacking a single clear etiologic agent identified as a microbiological enemy. Whatever the reasons, it means that an important cause of human suffering is relatively underserved. Because the burden of disease is so substantial, greater efforts designed to elucidate the biology of lung infections, to generate novel therapeutic or prophylactic strategies, and to better deliver interventions to needy populations have the potential for tremendous public health impact.

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# Pleural Fluid pH

The following information is based on the article "Prognostic Value of Pleural Fluid pH in Malignant Epithelial Mesothelioma after Talc Poudrage" by Yossef Aelony, Janis Yao and Randel King. Aelony and King are with the Department of Internal Medicine, Kaiser Permanent, Harbor City, CA. Yao is with the Southern California Permanente Medical Group, Pasadena, CA. Information for the article is redacted from "Prognostic Value of Pleural Fluid pH in Malignant Epithelia Mesothelioma after Talc Poudrage," Respiration 2006;73:334–339, Copyright © 2006 S. Karger AG, Basel, Switzerland, E-Mail karger@karger.ch Accessible online at: Rancho Palos Verdes, CA 90275 (USA) www.karger.com, www.karger.com/res. Information provided to Respiratory Therapy by Roche Diagnostics.

According to a recent article in Respiration (see above), current staging schemes for malignant mesothelioma are inadequate. The most accurate staging may require pneumonectomy. The authors note, "Low pleural pH (ppH) has long been correlated with poor outcome in patients with malignant pleural effusion. The mechanism of low ppH in advanced malignant disease is believed to be related to increased metabolism by pleural cells, decreased glucose transport into the pleural fluid, and a diffusion block of $CO_2$ efflux out of the pleural space. Under these conditions, lactic acid and hydrogen ions accumulate in the pleural fluid. This lower ppH has been directly correlated with the extent of tumor visualized thoracoscopically and with shorter survival."

The study by Aelony et al determines that ppH predicts survival in neomesotheliomatous malignant pleural effusions, suggesting that this noninvasive test might be useful for prognostication in malignant mesothelioma. Aeolony's study was to determine whether baseline ppH correlates with survival in malignant epithelial pleural mesothelioma. The authors reviewed survival data in patients treated with thoracoscopic talc pleurodesis where the final diagnosis was epithelial malignant pleural mesothelioma and charting recorded a ppH determination performed just before thoracoscopy. The authors monitored 26 patients, of whom 25 ultimately died, identifying cutoff ppH values that discriminate best for survival. The mean follow-up time was 19 ± 14 months, mean ppH was 7.30 ± 0.09, and median ppH was 7.32. ppH 7.32 was associated with the greatest survival value. Patients with ppH less than 7.32 lived a median of 21.2 months after diagnosis compared with patients who had ppH ≤ 7.32 and lived a median of 13.4 months. The baseline ppH correlated with survival in epithelial mesothelioma patients treated palliatively with pleurodesis by thoracoscopic talc poudrage. The authors recommended that this noninvasive ppH test should be included when staging patients with malignant mesothelioma.

## BACKGROUND

Little data exists on ppH and malignant mesothelioma. Patients were typically diagnosed by closed needle biopsy, and pathologists considered the amount of specimen obtained to be inadequate for reaching a definite diagnosis. Limitations on information garnered (low rate of confirmed diagnoses, inadequate tissue typing) resulted in a lack of adequate association between ppH and survival. Aelony and Yao had previously reported treatment results of palliative thoracoscopic talc poundage, though the results weren't statistically significant. The current study was designed to determine if the pathoracoscopic ppH in a combined group of 26 patients from Aelony and Yao's study correlated with duration of survival after the procedure.

For more than 20 years, Kaiser patients with recurrent symptomatic pleural effusion had received thoracoscopy for diagnostic biopsy, talc pleurodesis, or both. These patients' medical data were incorporated into a prospective database. A review of these data formed the basis for this study. Measurement of ppH was considered noninvasive because it is derived from fluid that would be sampled in any event. Baseline ppH was measured in fresh pleural fluid under anaerobic conditions, obtained before the induction of the pneumothora, prior to thoracoscopy. The ppH was measured using an AVL Scientific blood gas analyzer. Pleuroscopy with a parietal pleural biopsy and talc insufflation was performed using a rigid telescope with a single-puncture technique. Microscopic analysis was performed by our own pathologists and confirmed by the US-Canadian mesothelioma panel.

To identify a cutoff ppH value that defined a warning level for survival in the data, the researchers used the 18-month follow-up data, which provided sufficient information. Adjusted ROC curves were recursively run using the same ppH cutoff values and were adjusted by age and side of lung affected.

## ppH VALUES AND SURVIVAL

Results indicated that ppH values were significantly associated with survival. Associations of either side of the lung affected and age with survival were borderline significant. The median survival for patients with ppH >7.32 was 21.2 months versus 13.4 months for ppH ≤ 7.32. The study revealed that ppH was the only significant factor.

Patients were treated by the same approach, using thoracoscopic talc pleurodesis as the primary palliative modality of care. Three patients were subsequently treated with chemotherapy and radiation therapy and survived a mean of 10.5 ± 3.1 months. After receiving talc poudrage, the patient with ppH 7.26 survived 12.5 months, the patient with ppH 7.27, 14.6 months, and the patient with ppH 7.19, 4.5 months. The other 23 patients received no antineoplastic treatment before or after receiving pleurodesis.

As this series demonstrates, the relation of ppH to survival in patients with malignant effusion also applies to patients with epithelial malignant mesothelioma when the main treatment is palliative thoracoscopic talc pleurodesis. Management was basically the same for all patients. Overall survival in this group of patients was relatively good compared to other approaches.

Aelony et al noted that the ppH prognostic factor is likely to be important regardless of the type of subsequent treatment received, but because the sample size in this study was small, the optimal ppH cutoff point might not be representative, and suggested that a multicenter study would be necessary to collect a large enough series to achieve statistical significance for less frequent subtypes of mesothelioma.

All patients in this study had large effusions (>1,000 ml). Staging proposals could not be applied using a retrospective record review and current surgical staging seems inapplicable for thoracoscopy patients. Recent editorials have decried the unavailability of uniform, effective staging schemes in mesothelioma.

The authors noted that prospective studies with multivariate analysis are needed to determine whether ppH functions independently of these other factors, and awaited information from the European Organization of Research and Treatment of Cancer and the Cancer and Leukemia Group B staging programs which could then be combined with ppH, PET scan intensity and tumor necrosis grading, leading to prospective studies showing correlation with survival.

The authors concluded, "Research efforts should now focus on incorporating ppH into disease staging for all mesothelioma patients. Ideally, controlled studies would always be conducted comparing various modalities of treatment… and including a control group of patients receiving best supportive care. Notwithstanding those studies, improved staging is essential to allow prognostication for the patient, to permit better comparisons between phase II studies, and to facilitate selection of patients for future prospective trials."

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# Pleural Fluid pH Analysis in the Blood Gas Laboratory

This article is specifically addressing the role of the Respiratory Care Practitioner (RCP) in the role of body fluid analysis and specifically pleural fluid pH. Before we take an in depth look at this analyte we must first look at the pathophysiology of this pneumonic process.

Pleural effusion is the accumulation of fluid in the chest between the lung and the chest cavity. Normally there is no space between the parietal pleura, which covers the chest wall, and the visceral pleura, which covers the lung. The normal fluid that is present facilitates the mechanics of ventilation that maintains a negative intrapleural pressure therefore allowing the lungs to remain expanded. For a diagnosis of pleural effusion, 75% of those patients will have a diagnosis made at the onset of the clinical findings presented. 25% of those patients will have a positive cytology or positive culture of the aspirate analyzed. Fifty percent of those patients have a presumptive diagnosis

prior to the laboratory findings. Fifteen to 20% of the patients will not have a diagnosis made prior to diagnostic studies. The history and physical (H & P) exam are critical in guiding the evaluation of the pleural effusion and it is imperative that an extensive H & P be obtained from the patient. Chest examination demonstrates dullness to percussion and diminished breath sounds, which may be, but are not necessarily gravity dependent. Confirmation of a pleural effusion may include an Anterior-Posterior radiograph, lateral decubitus whereby the patient lays on their side, and/or CT of the chest and abdomen. The interpretive physician is looking for clear radiographic findings that suggest a pleural space infiltrate. The definitive diagnosis is a thoracentesis whereby the physician performs a needle aspirate to a local anesthetized area of the chest wall and inserts the needle into the pleural space now occupied by an infiltrate. The sample must be obtained under anaerobic conditions, iced, and analyzed within two hours preferentially through the "gold standard" Blood Gas Analyzer (BGA). If the sample is not iced, in vitro glycolysis will occur resulting in a false low pH. If the sample is exposed to room air, then a false high pH will occur due to gas equilibration. The sample, by most clinical standards of medical practice, should include a diagnostic order for LDH, Protein, Glucose, Amylase, Cell Count, Cytology, and cultures in addition to pH analysis. There are about 1 million cases per year of pleural effusions and primarily are subcategorized as transudate (movement of fluid into the pleural space due to imbalance of hydrostatic and oncotic pressures) or exudative (caused by inflammation of the lung or pleura) effusions. Trasudative effusions normally have a pH 7.40-7.55 and exudative effusions normally have a pH less than 7.45. Categorically, most of the effusions are by congestive heart failure, malignancy, infections, and pulmonary emboli, requiring urgent evaluation and treatment. It is interesting to note that 25% of the pleural effusions are resolved within 48 hours with aggressive diuretic therapy. Cirrhosis, pulmonary embolus, infection, malignancy, immunologic disorders, lymphatic abnormalities, non-infectious inflammation and nephritic syndrome are other common etiologies of transudative pleural effusions. Decreased glucose in the pleural fluid may indicate a malignancy, empyema, and a complicated parapneumonic effusion, or tuberculosis to name just a few disease entities. Normal pH of pleural fluid is 7.60. American College Chest Physicians (ACCP) and the British Thoracic Society agree that pH values less than 7.20 are a critical value with a parapneumonic infection and will require immediate drainage via chest tube insertion. 20-25% of pneumonia patients have a parapneumonic infection and will resolve with aggressive antibiotic therapy. Decreased glucose with a decreased pH signals the possible diagnosis of a malignant pneumonic process. A pH less than 7.28, with a malignant pneumonic process, has a 39% mortality after 3 months. Two negative cytologys with a low pH indicate possible tuberculosis or rheumatoid pleurisy.

Several analytical methods have historically been performed over the years. The methods that have been and currently are being utilized are the pH meter, pH indicator strips, and the Blood Gas Analyzer (BGA). In studies reported in Chest (1998), pH meters and pH indicator paper reported significantly higher mean pH than the BGA; therefore the clinical and research findings as stated earlier in this article were that the BGA is the gold standard for pleural fluid pH analysis. Blood Gas Laboratories must meet regulatory standards as set forth by CLIA and other regulatory agencies such as College of American Pathologists (CAP). The method of testing falls into three CLIA classifications of waived, moderately complex, and highly complex categories. The BGA fall into either the moderately complex or high CLIA complexity category depending upon whether the BGA has undergone 510K FDA clearance for analyzing pleural fluid pH. It is each laboratory's responsibility to determine if their BGA has met the FDA clearance for analyzing pleural fluid pH. If your instrument is 510 K FDA cleared, then CLIA recognizes this instrument's analyte as a moderately complex instrumentation. If the BGA is not FDA cleared which is referred to as "off-label," then the analyte is considered to be reported from high complexity instrumentation and must meet the 6 point high complexity CLIA category. Pleural fluid pH analyte reported from a moderate complex BGA has less regulatory requirements from CLIA as opposed to an "off-label" BGA that must meet more CLIA regulations. CLIA does not recognize the waived category for pleural fluid pH so to use litmus paper you must meet CAP guidelines of proficiency testing, daily QC, method validation, and personnel training and competency validations. The use of litmus paper is compromised by the fact that the test results cannot be reported in hundredths (X.XX) and the accuracy needs to be reported to this mathematical expression, as accuracy is the critical factor in reporting pleural pH. Litmus paper relies on colorimetric determinations and has a falsely reportable high value as previously mentioned in Chest. PH meters expose the anaerobic sample to room air and have falsely high reportable pH as well. Pleural fluid samples when analyzed through the BGA should be cautiously analyzed with the addition of a clot catcher between the syringe and the BGA sample inlet port or an internal clot catcher as the pleural sample presents a small risk of BGA clotting contaminates much like other blood samples introduced into a BGA such as neonatal or patients with polycythemia. Critical values must be determined to meet CAP standards and documented like any other critical value in your laboratory. We have established any value less than 7.20 as a critical result and must be called and read back to the ordering physician to meet CLIA, CAP, JCAHO, and other accreditation standards.

Body fluids must meet proficiency testing just like any other analyte and can be ordered from the CAP web site. These are performed twice a year and reported using similar proficiency testing methodologies.

In summary, pH pleural fluid testing provides the physician with a valuable diagnostic test that complements the clinical decisions necessary to provide excellence in patient outcomes. Not only does the diagnostic testing provide a diagnostic tool, but also from the financial aspect it is a revenue stream within your departmental operations.

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# Why use a blood gas system with FDA 510(k) clearance for pleural fluid pH testing?

The College of American Pathologists and articles in *Chest* cite blood gas analyzers as the "method of choice" for measuring pleural fluid pH,[1,2] and only one analyzer is FDA-cleared to help you achieve regulatory compliance: The **cobas b** 221 blood gas system.

Pleural fluid pH can be a clinically useful tool for managing patients with pleural effusions—and can be especially important in critical care environments such as the ED.

**Only the cobas b 221 blood gas system is FDA 510(k)-cleared for pleural fluid pH testing.**

Roche Diagnostics

# Bilirubin Determination Using the Roche OMNI S Point-of-Care Analyzer

Information for this article appeared in another format in Point of Care Volume 4, Number 1, March 2005, © 2005 Lippincott Willliams & Wilkins. The authors are Boris Rolinski, MD; Anthony Okorodudu, PhD; Gerald Kost, MD; Markus Roser, MD; Jiaxi Wu, MD, PhD; Ada Goerlach-Graw, PhDk; and Helmut Kuester, MD. The article was provided for publication in Respiratory Therapy by Roche Diagnostics.

According to the Symposium Article, "Evaluation of Total Bilirubin Determination in Neonatal Whole Blood Samples by Multiwavelength Photometry on the Roche OMNI S Point-of-Care Analyzer," jaundice is a common finding in healthy and diseased neonates. Because of early discharge, the risk of kernicterus is a reemerging problem in the US. Precise and accurate determination of plasma total concentrations is indispensable for proper management of jaundiced infants. In their multicenter study, Rolinski, et al investigated the analytical performance of the Roche OMNI S blood gas analyzer for measurement of total bilirubin from neonatal whole blood using a multiple-wavelength photometric method. Results were compared to other results from routine clinical chemistry methods and another device. Four hundred and ninety-six heparinized blood samples were drawn from newborns of 39 days or less. An aliquot of the whole-blood sample was measured on the Roche OMNI S and on the Radiometer ABL 735. Plasma bilirubin concentrations covered the diagnostic relevant range up to 23.7 mg/dL. There was good agreement between the bilirubin concentrations measured in whole blood on the Roche OMNI S and Radiometer ABL 735 and between the comparison routine analyzers. Correlation coefficients were above 0.94, and the slope of the regression lines ranged from 0.971 to 1.172. The mean biases ranged from –0.3 to 1.4 mg/dL, and the differences between comparison methods were less than those reported in proficiency testing. Direct spectrophotometric measurement of bilirubin in neonatal whole-blood samples gave results that compared well with those obtained using routine chemistry methods. Noted advantages were the very small volume of blood and the short turnaround time. The authors of the study concluded that the Roche OMNI S analyzer represents a suitable method for monitoring neonatal jaundice at the point of care.

## BACKGROUND

In the newborn, hyperbilirubinemia is due to an increased hemoglobin turnover along with immature hepatic glucuronidation. Neonatal jaundice is a common finding insofar as about 60% of infants become clinically jaundiced in the first week of life, and about 33% of breastfed infants have total bilirubin levels above 12 mg/dL. Plasma bilirubin concentrations in neonates can range as high as 40 mg/dL. Newborn jaundice is usually considered benign, with hyperbilirubinemia resolving within the first week, but in rare cases, higher concentrations of bilirubin may cause kernicterus. While the condition is considered rare due to prompt postnatal medical care, reports have shown an increasing frequency. Because phototherapy or exchange transfusions may be required to lower bilirubin concentration, therapeutic decisions must rely on determining plasma bilirubin concentration. As such, babies with jaundice are typically monitored for bilirubin levels from four hours a day to every other day. Thus, it's desirable to employ methods that come up with quick and reliable results, using small volumes of whole blood. Recently, the Roche OMNI S blood gas analyzer was equipped with the same feature as the first instrument to provide total bilirubin determination in whole blood, manufactured by Radiometer.

## MULTICENTER STUDY

The study was conducted in four hospitals with NICUs, in California, Texas and Germany. Four hundred ninety-six heparinized blood samples were analyzed, using samples from 353 newborns ranging in age up to 39 days, with a median age of 4 days. An aliquot of whole blood was measured on the Roche OMNI S or the Radiometer ALB 735, and plasma was prepared from the remaining sample. Total bilirubin in plasma was measured by wet chemistry, and a total of ten sets of comparison data were obtained. One set of samples was also measured for direct bilirubin and for serum indices by direct photometry. Various methods were used to assess imprecision, inaccuracy and recovery, and heparinized whole-blood samples were obtained from healthy volunteers. The hematocrit was measured on the Roche OMNI S and the plasma volume calculated. The samples were centrifuged, and a portion of

plasma supernatant was replaced by an equal volume of bilirubin stock solution to provide desired plasma concentrations of 6, 24 and 48 mg/dL, after which samples were re-dispersed and used for immediate bilirubin measurement on the Roche OMNI S. Fresh samples were prepared daily. Control samples were prepared by dilution in albumin solution or bovine serum albumin fraction V, or in human pool plasma with low bilirubin concentrations to give final bilirubin concentrations of 0,2,10 and 20 mg/dL and 0.8, 2.8, 10.8 and 20.8 mg/dL for albumin-based and plasma-based samples, respectively. The samples were aliquoted and stored until analysis. Recovery on the Roche OMNI S was investigated at two sites with a set of 10 accuracy controls ranging from 1 to 13 mg/dL bilirubin.

## RESULTS

Plasma bilirubin concentrations ranged from 0.2 to 23.7 mg/DL, which covered the range for proper diagnostic decisions. Hemoglobin concentrations varied from 10 to 23.6 g/dL. Agreement was good between bilirubin concentrations measured in whole blood on the Roche OMNI S and measured from comparison methods. The mean correlation coefficient was 0.966 +/- 0.015 and the mean slope of the regression lines was 1.047 +/- 0.052, with mean intercept of –0.065 +/- 0.523. Mean bias was 0.41 +/- 0.51 mg/dL.

The authors observed a slight offset between the same Roche 2,5-DPD method in two of the German settings, with recorded values slightly higher and lower, respectively than those of the OMNI S. The difference remained unexplained, but evaluation showed that the Roche DPD method fit correctly with the Roche OMNI S. The rest of the wet chemistry methods also correlated well with the Roche OMNI S, except for the neonatal bilirubin run in Munich. The method is a direct photometric reading from the sample diluted in buffer at two wavelengths, with recorded values about 10% lower than those obtained with DPD. According to the authors, the method suffers from interference by hemolysis and turbidity more than methods based on reaction with diazo dyes. As such, according to Rolinski, et al, direct photometry at two wavelengths is inferior to all other methods tested in the study, and discrepancies can be attributed to this problem rather than to methods employed. Dry chemistry bilirubin correlated closely with the Roche OMNI S whether compared with values obtained with TBIL or BIL slides. Comparison of the Roche OMNI S with the Radiometer ABL 735 showed an offset of 1 mg/dL between the instruments, which the authors found odd insofar as both instruments rely on direct multiwavelength photometry. It was surmised that the discrepancies may have occurred in the calibration process, from the calculation algorithm, or from differences in compensating the hemoglobin interference.

Outliers defined as a relative bias of >21% were observed, with the highest number at one of the German sites. It was speculated that perhaps the Roche analyzer employed at that site was less reliable than the others, but it wasn't possible to repeat the measurement due to sample limitations. However, differences between methods were found to be minor and much less that differences typically reported in daily routine or proficiency testing surveys.

Results of quality control studies revealed that precision and accuracy were well within the specified ranges of the instruments. Precision and bias for whole-blood controls were less accurate, but sample preparation would have contributed significantly to the imprecisions noted. Recovery of the 10 commercial accuracy controls based on plasma matrix was good, with a bias from –0.13 to 1.23 mg/dL. No difference was observed between the control materials.

The authors note that quality control is a difficult issue for methods using whole-blood samples, and, until now, the problem of matrix conformity of quality-control material had been unresolved. This is why different matrices were used in the study. The Auto Trol material used for the Roche OMNI S is a photometer control based on dyes in aqueous solution and doesn't contain bilirubin. The researchers used commercial and in-house quality-control material based on serum matrix, with the advantage that this material contains the real analyte and is stable for within-day experiments. Whole-blood controls were also used but had to be prepped daily, which increases imprecision and isn't feasible for clinical routine.

## CONCLUSIONS

According to the authors, "Measurement of bilirubin is know as one of the most unreliable tests in clinical chemistry." Until recently, no accepted reference method existed and no standardization between assays of different reagent suppliers had been achieved. As such, there have been no true values to rely on for comparison studies or for the care of patients, and target values for control materials may vary widely, depending on the assay. Rolinski et al conclude, "Taking this into consideration, our study clearly demonstrates that the accuracy and precision of the Roche OMNI S analyzer meets the expectations for routine laboratory method and allows for the reliable determination of bilirubin concentrations in neonatal whole-blood samples. Advances in laboratory medicine are often driven by the need to obtain more information from a smaller sample at a faster time than previously possible. Especially for monitoring hyperbilirubinemia in the newborn, direct photometry of neonatal whole-blood samples in a blood gas analyzer provides fast yet reliable results from very small sample volumes, enabling bilirubin measurement at the point of care."

# Accuracy of near-patient testing of bilirubin and haematocrit measurement With Omni S blood gas analyser

P K Dey[1], S Pattnayak[1], B Bewley[2], A MacDonald[2], A W Kelsall[1]

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## INTRODUCTION

Near-patient measurement of blood gases, electrolytes and bilirubin have been performed in neonatal intensive care units (NICU) [1, 2].

Advantages include:

- Multiple assays on smaller blood volumes
- Immediate access to results
- Less handling and trauma to babies
- Long-term reduction in blood transfusions
- Less risk of needle stick injury
- Less equipment

## AIM OF THE STUDY

To compare bilirubin and haematocrit measurements from Omni S analyser with Bilimeter II and micro-haematocrit reader

## METHODS

Blood samples were collected in heparinised capillary tubes (maximum 200 µL) for blood gas, bilirubin and haematocrit measurement using Omni S analyser.

Simultaneously blood samples were collected in 75 µL heparinsed capillary tubes & centrifuged for 3 minutes (Centurion Scientific instrument).

Bilirubin assays were performed with Bilimeter II (Pfaff Medical). Haematocrit measurements were done using Hawksley micro-haematocrit reader.

(No additional blood samples were taken)

Statistical analysis was performed using method validator software.

Fig1 Omni S analyzer

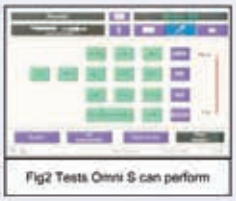
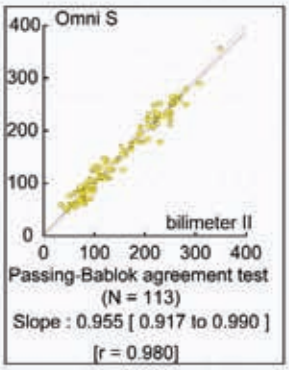


Fig2 Tests Omni S can perform

## RESULTS

**Fig 3 & Fig 4 show comparisons of bilirubin measurements between Bilimeter II & Omni S**



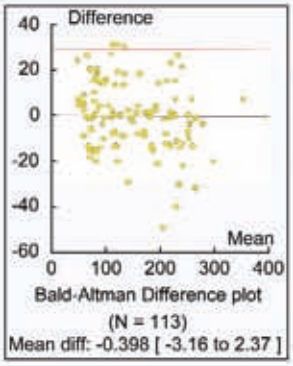
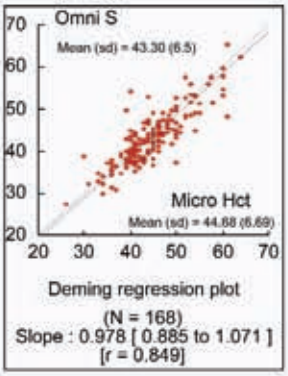
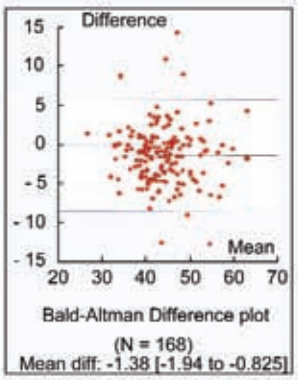




**Fig 5 & Fig 6 show comparisons of haematocrit measurements between micro-haematocrit reader & Omni S**




## CONCLUSIONS

**Bilirubin & haematocrit assays can be successfully measured from single blood sample using the Omni S analyser. This system results in reduced blood sampling and simplified equipment requirements on NICU.**

## REFERENCES

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# Why is a 1-minute bilirubin test especially important in the NICU?

Timely monitoring of critical newborns can reduce the risk of potentially life-threatening diseases and enhance neonatal care for hyperbilirubinemia.

*Kernicterus* is a serious condition that can occur in infants with elevated bilirubin levels (>20 mg/dL).[1] The **cobas b** 221 blood gas system can help reduce the risk of kernicterus by delivering fast, actionable bilirubin results in the NICU.

**The cobas b 221 system delivers bilirubin results in 1 minute or less.**

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# Blood Gases – A Clinical Primer

Information in this article is from "Clinical Blood Gases, Application and Noninvasive Alternatives," by William J. Malley, MS, RRT, CPFT, Program Director, School of Respiratory Care, Indiana University of Pennsylvania, Indiana, PA, in cooperation with West Penn Hospital, Pittsburgh. The original text appears in the chapter by the same name, W.B. Saunders Company, an imprint of Elsevier Science, © W.B. Saunders Company. Material herein is provided by Roche Diagnostics.

According to William Malley, writing in *Clinical Blood Gases*, mechanical ventilation has the potential to camouflage acid-base events. Many therapueutic measures can lead to iatrogenic acidic-based disturbances. "Arterial blood gases and acid-base disturbances must always be interpreted within the context of therapeutic measures and long-standing pulmonary or renal disease." Malley writes that the natural tendency of the body is to compensate for primary acid-base disturbances. Because of this phenomenon, whenever opposing respiratory and metabolic conditions are present, compensation is assumed. Although this initial assumption is logical, it is often incorrect. It is not uncommon to have two opposing primary acid-base disturbances that give the surface appearance of simple compensation. The coexistence of two primary acid-base disturbances is called a mixed acid-base disturbance.

How can simple compensation be differentiated from a mixed acid-base disturbance? Probably the most useful aid in this regard is an acid-base map. When a patient's values fall outside established parameters, it is very unlikely that the patient has had just one disturbance. Any acid-based mapping doesn't necessarily mean that elevated bicarbonate can't be due to a primary problem, but only that data are consistent with usual compensation for early respiratory acidosis. Without an acid-base map one might assume that certain blood gas results are due to complete compensation. An acid-base map is a simple, useful tool for the evaluation of mixed acid-base disturbances. Durable pocket acid-base maps are available from the Christmas Seal League/American Lung Association Affiliate, Pittsburgh, PA.

As Malley notes, some types of acid-base problems, like metabolic alkalosis, result in more complete compensation than others. As such, it is useful to have some idea of the typical compensatory patterns that should accompany the four simple acid-base disturbances. This can help the clinician to evaluate the appropriateness of the degree of compensation observed in a given individual.

In respiratory acidosis, the pH falls approximately 0.06 unit for an acute 10 mm Hg increase in $PaCO_2$. After maximal renal compensation, the change in pH associated with an increase of 10 mm Hg in $PaCO_2$ is approximately 0.03 unit. Thus, the pH returns approximately 50% of the way back toward normal after maximal compensation. For example, when the $PaCO_2$ increases to 70 mm Hg acutely, the pH drops immediately to approximately 7.22 (0.06 decrease/10 mm Hg $PaCO_2$ increase). The immediate increase in bicarbonate is a result of the hydrolysis effect that was discussed in Chapter 8 and it does not represent renal compensation.
After maximal renal compensation, however, the pH returns approximately half-way back to normal. Thus, complete compensation is not usually seen when respiratory acidosis is so severe. Complete compensation for respiratory acidosis occurs only when the respiratory acidosis is not severe. Also, because the mechanism of renal compensation for respiratory acidosis is bicarbonate retention, the chloride anion is typically low to preserve electroneutrality.

Compensation for respiratory alkalosis is similar in magnitude to compensation for respiratory acidosis. In general, the pH should return at least half-way back toward normal. However, when the respiratory alkalosis persists, the pH may actually return completely to normal in some cases. Renal compensation for respiratory alkalosis requires the excretion of bicarbonate; therefore, hyperchloremia often develops to preserve electroneutrality.

In cases of metabolic acidosis, increased ventilation response often begins quickly, but maximum response may take a full day. When metabolic acidosis develops in the plasma, it takes some time for the pH to fall in the cerebrospinal fluid owing to the

limited permeability of ions across the blood-brain barrier. Lactic acidosis, however, may actually develop within the brain cells, and it is therefore associated with a more rapid ventilatory response. As Malley notes, "a very useful rule of thumb is that after maximal compensation, the $PaCO_2$ generally approximates the last two digits of the pH. Thus, in simple chronic metabolic acidosis with a pH of 7.30, the $PaCO_2$ is usually about 30 mm Hg.

In cases of metabolic alkalosis, the respiratory compensation is hypoventilation with retention of carbonic acid. It used to be assumed that this response was limited by the onset of hypoxemia. Therefore, it is often stated that compensation for metabolic alkalosis will not allow the $PaCO_2$ to exceed 55 to 60 mm Hg.

However, recent evidence has indicated that hypoventilation is not limited by hypoxemia. "Progressive, linear hypoventilation accompanies progressive, simple, metabolic alkalosis when it is not associated with other acid-base problems," per Malley. "Compensation may sometimes also allow the pH to return half-way back to normal; however, a lesser compensatory response is more common."

Malley concludes, "In the absence of an acid-base map, it is useful to know that maximal compensation for most simple acid-base disturbances is approximately 50%. Compensation for respiratory alkalosis is usually slightly greater than this, whereas compensation for metabolic alkalosis is usually slightly less. Knowledge of compensatory patterns can alert the clinician to the presence of a mixed disturbance even when an acid-base map is not at hand." His conclusion adds the coda, however, that mixed acid-base disturbances are common in the hospital setting. "When primary acid-base problems are camouflaged in mixed disturbances, they may easily be missed. In this setting, covert acid-base problems are untreated and are likely to lead to progressive deterioration. Furthermore, even use of the acid-base map does not identify those mixed disturbances that result in blood gas data that coincide with findings that normally accompany simple disturbances."

## BLOOD GAS LEVELS

I. Here is an example of blood gas levels that may be recorded during mechanical ventilation for a patient with metabolic acidosis: pH: 7.44, $PaCO_2$:18 mm Hg, [BE]: -12 mEq/L, $[HCO_3]$:12 mEq/L, $PaO_2$:64 mm Hg. Regarding these levels, Malley notes, "this patient has only a metabolic acidosis. Nevertheless, the rapid respiratory rate generated as a compensatory mechanism to the acidosis, in conjunction with the delivery of large tidal volumes via mechanical ventilation, has caused the apparent alkalosis. It would be inappropriate, however, to attempt to treat the respiratory alkalosis. The only true primary acid-base problem in this patient is metabolic acidosis. Mechanical ventilation has created the false impression of respiratory alkalosis."

II. Here's an example of blood gas levels that may be recorded for metabolic acidosis during spontaneous breathing: pH: 7.32, $PaCO_2$: 25 mm Hg, [BE]: -12 mEq/L, $[HCO_3]$:13 mEq/L, $PaO_2$:64 mm Hg.

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# How can automated acid-base mapping help you deliver a more precise diagnosis and therapy monitoring?

Accurate, graphical acid-base mapping on the **cobas b** 221 blood gas system can help clinicians:

- Rapidly identify metabolic and respiratory acid-base disturbances without the need for a calculator
- Efficiently assist physicians to monitor the effectiveness of therapy
- Easily distinguish between compensatory responses and mixed acid-base disturbances
- Differentiate between acute and chronic patient conditions in complex environments such as the ED or ICU

**Automated acid-base mapping on the cobas b 221 system creates a graphical representation of patient results.**

Roche Diagnostics

# Roche Diagnostics

Rodney D. Cotton

Rodney D. Cotton, Senior Vice President, Point of Care Diagnostics

**PRODUCT PROFILE**

The Roche OMNI S blood gas analyzer offers a significant advantage for both patient and care-giver by decreasing the sample size required. This is especially important in NICU. By offering Neonatal Bilirubin in or close to the NICU you can reduce the turn around times and improve the time it takes to deliver therapeutic interventions.

Roche Diagnostics' Auto QC system option helps to improve operator efficiency, thus resulting in additional time available for patient care. It also makes it easier to meet ongoing regulatory requirements. Roche Diagnostics' industry leading IT solutions help to regulate operator validation, quality oversight, help to manage cost and assure that clinical data is transferred to the LIS/HIS system for cost capture and reporting.

Roche Diagnostics' blood gas systems offer improved operator interfaces. This helps to improve operator effectiveness and efficiency thus providing for more time directly with the patient.

"MyLabOnline" service is a web portal for Roche Diagnostics product users. It empowers them to improve their operational efficiency via product and clinical information. In addition it provides real-time data on order status and peer-review QC statistical performance information.

eQAP – This is another Roche Diagnostics first. The eQAP program, available via "My LabOnline" permits customers to enter their QC results and have the data analyzed and eQAP, as the Roche Diagnostics first, enhances customers' confidence in the results they are reporting by availability of real-time peer reviewed data on their QC results This complimentary service facilitates our customers to compare their performance to others across the country in real-time.

**ADVANCES AND IMPROVEMENTS**

Major improvements in BGE testing include: NICU/ICU advantages—availability of neonatal bilirubin, and reduced sample size vs. lab method. The overall benefits of the Roche Diagnostics BGE portfolio are reduced complexity (operation and maintenance); and automated QC. Roche Diagnostics is the gold standard and the industry's first BGE analyzer with an Auto QC option. Today, we still maintain an advantage by offering 40 days of on-board QC material. For IT/data management, Roche Diagnostics provides hospitals with the industry's best blood gas work flow management solution with its Data Care software. Roche Diagnostics also launched the industry's first complete remote QC/Instrument status management software (OMNILINK).

Another first for Roche Diagnostics is that it has again led the industry by recently gaining the first 510k clearance for measuring pH in pleural fluids on blood gas analyzers. It is reported that over 1 million pleural effusions are diagnosed in the US each year. At present, the College of American Pathologists reports that over 68% of the analyses are performed via pH paper or pH meter. The American College of Chest Physicians reported in 1998, "When pleural fluid pH is going to be used for decision making, only pH values provided by blood gas machines are sufficiently accurate."

**R&D & EDUCATION**

Roche Diagnostics runs major R&D projects through a Global Portfolio Board for review approval and status update. Continued project improvements are evaluated and submitted for consideration on an ongoing basis. Input is strongly driven by input from customers (current and potential).

Roche Diagnostics' Annual Teleconference offers PACE & AARC accreditations. Its "My LabOnline" web portal provides on-line access to PACE & AARC accredited programs. Roche Diagnostics also offers educational workshops to national and regional meetings. At Roche Diagnostics, product upgrades, enhancement and new product designs are the combined result of input from advisory panels, visionary thought leaders and market research. For new product launches, Roche Diagnostics will run "Gamma Site" trials (these are beyond what is required for 510k submission). These studies provide us with greater insight as to work flow, positioning and impact to hospital patient care and hospital economics.

Roche Diagnostics is actively working on the development of new technology that will significantly reduce operator "hands-on time." We will broaden our IT portfolio and will deliver systems with the configuration flexibility to fit into all clinical areas where BGE is needed. All of the above will be delivered with continued focus on improved patient care and cost effectiveness.

**NEW TECHNOLOGY**

The most significant change that is currently occurring is the expansion of IT connectivity and DM. Also electronic miniaturization continues to drive reductions in size and weight while increasing reliability and reducing maintenance requirements and down time.

Examples of Roche Diagnostics' leading technology are: Omni Link (QC and device management software), DataCare (BGE data management and IT connectivity software), Smart Pack Technology (for reagent matching and expiration control), Auto QC (time saving automated QC option) and "O" Maintenance Electrodes (more time focused on patient care).

All hospitals and clinical sites can benefit from the Roche Diagnostics BGE technology. However, respiratory therapists in the ICU NICO can significantly improve their patient care, work flow and operational efficiency by using the Roche Diagnostics BGE/IT portfolio.

Roche Diagnostics is clearly a global organization. However, we strongly believe that we must plan globally, yet deliver and implement locally. The US has a very strong input into global portfolio decisions with representation on the global portfolio book.

Roche Diagnostics will continue to use multiple methods to communicate our message and capture customer input. First, we will continue to have focused and dedicated sales teams for both BGE and IT. Second, we will continue to provide on-site training and technology support complemented by 24-7 telephone coverage. Third, Roche Diagnostics will continue to attend national and regional professional conferences. Fourth, we will continue to offer user centric web portals and services such as "MyLabOnline" and eQAP. Additionally we will utilize focus panels and advisory board to help us best formulate and deliver key product and service messages to our customers and market in general. (Roche OMNI, Auto QC, MyLabOnLine, DataCare POC and OMNILINK are trademarks of Roche.)

# Blood Gas Technology

Ken Levy, Director of Hospital Point of Care

**How has technology in blood gas measurement and reporting changed over the past 10 years?**

The fundamentals of measuring and reporting blood gas parameters have not changed significantly. What has changed is analyzer technology. Today's blood gas analyzers are more reliable, smaller and easier to maintain and use. The use of state-of-the-art electronics, improved user interfaces and Information Technology has helped respiratory therapy departments and the Lab keep pace with the increasing regulatory and quality requirements. For example: In the case where the lab "owns" the CLIA license, but the respiratory department performs the blood gas analysis, the use of IT products like Roche's OMNILink software permits the lab to review the calibration and QC status remotely. OMNILink also allows the lab to remotely monitor the analyzer's reagent supply, thus helping to prevent downtime during critical periods. Remote control and monitoring of operators' eligibility and performance, plus the ability to review and print all required QC reports, helps the staff responsible for quality and regulatory oversight complete their tasks without going to each location where a blood gas analyzer is stationed. In addition to improvements in IT technology, the ability to perform blood gas analysis without the need for gas cylinders or filling and polishing electrodes and sensors has decreased maintenance time, thus permitting the staff to focus on direct patient care.

**How has your company led R& D efforts to continue improving this technology?**

Roche has been a technology leader and innovator in many areas. Roche offered the first non-maintenance electrodes and sensors, developed the first automated QC system, and leads the industry in blood gas analyzer remote control and quality management. In addition, Roche's OMNI S blood gas analyzers are the only system to utilize radio frequency to maintain analyzer-independent memory of reagent volume, lot number and expiration dates. This permits reagents to be moved from one analyzer to another, thus utilizing reagents more efficiently based on each analyzer's test volume.

**How have you streamlined your preventative maintenance and troubleshooting of analyzers?**

Roche Blood Gas analyzers only require a limited amount of routine maintenance. Regular maintenance (beyond reagent change) is scheduled in the analyzer's firmware, which notifies the operator or supervisor prior to the date that maintenance is due. Roche's maintenance-free electrodes and sensors also eliminate the work required to keep electrodes in peak performance. Not only are our electrodes maintenance-free, but the on-board life of our electrodes and sensors has set the standards in the industry. In addition, Roche Blood Gas analyzers under warranty or service agreement have scheduled preventive maintenance performed by factory trained Field Service Representatives. A new Roche offering is an online service, known as Axeda. Customers who have a Roche OMNI S system and the Roche DataCare POC and OMNILink software packages can have service techs remotely connect into the system and perform trouble-shooting 24 hours a day, 365 days a year. By offering this service, we will significantly reduce the time it takes to get trained eyes on the problem. Should a field visit be required, the technician will be prepared with the information and parts required to remedy the problem.

**What efforts have you made in automation?**

At Roche, we believe that there are tests where automation adds significant value and other areas where it is of minimal value. Roche is an industry leader in laboratory automation; however, based on feedback from our customers we believe that the real value in automation comes in the area of automating quality control and data management. Roche's auto QC modules and IT solutions for data management and remote control are the best in the industry. It is automation in these areas that we believe saves the most time, thus reducing the clinical staff's time away from the patient.

**Where do you see your product used most?**

As you know, blood gas analysis is needed in a variety of locations in the hospital. The industry average turnaround time for a blood gas analyzer is 15 minutes. This can be compared to almost 60 minutes for other laboratory tests. More than two-

thirds of the blood gas tests performed today are in a location outside of the central lab. Respiratory Therapy departments, emergency departments, ORs, ICUs and NICUs are examples of locations where requests for blood gas tests originate. Often there is a trade-off between moving the blood gas analyzer next to the patient versus the central lab or a STAT lab near the patient (decentralized site) and that trade-off is cost per test. Bench-top systems, although larger, can often produce blood gas, electrolyte and metabolite results at a fraction of the cost of hand-held or portable systems. Also, the ability to perform a broad selection of analytes on a single sample of blood favors the use of bench-top systems. Again, the need for speed (vein to brain time) should be the first criterion used when determining which system is best suited.

**How prevalent is point of care testing vs a centralized lab system?**

As noted earlier, in the US more than two-thirds of blood gas testing is performed in a decentralized setting. This is not the case outside the US, where most blood gas is still performed by the central laboratory.

**What type of training and customer support programs are in place?**

Roche offers a variety of training and customer support options. First, we perform on-site training of key operators and trainers. We also have key training video sequences located on each OMNI S blood gas analyzer. An operator may run through the operation of the analyzer and see each step performed as prescribed. Roche Operator Manuals also outline, in detail, the complete operation and maintenance of each analyzer. In addition, should customers have questions, they are directed to call the Roche Customer Support "hot line" 24 hours a day, 365 days a year. Should an on-site technical call be required, a trained service technician will be dispatched to the site. Roche also offers continuing education opportunities for its customers. The most recent offerings address pH measurements on pleural fluid and quality control measurement and reporting for Blood Gas.

**How do you assist customers with technical issues or compliance issues when possible?**

Roche offers a variety of support mechanisms to assist our customers with technical and compliance issues. First, we offer 24-hour, 365-day technical phone support. Due to Roche's size and large customer base for chemistry and immunochemistry analyzers, we have a field service support organization that is best-in-class. Over 300 field service technicians are distributed across the country and available on-site to address technical issues that can not be addressed remotely via telephone or through Axeda, our newest on-line support tool. In addition, we also offer self-help via MyLabOnline. Customers may login to MyLabOnline and look up technical bulletins and MSDS information. We also offer customers, at no charge, "eQAP," which is a real-time, online quality control review service that lets customers perform peer-review analysis and print out quality control statistics and reports needed for CAP or JCAHO requirements.

**How do you view your relationship with the end user of your product?**

Roche views our relationship as a true partnership. We and our customers are in the business of improving healthcare and the quality of life. The Roche Point of Care Diagnostics Mission Statement says it all: *"Our passion is to shape the future of Diagnostics through leading solutions that empower immediate healthcare decisions to improve quality of life."* We look to our customers to provide us with open and honest input on how we can continue to improve our products and services. We ask and listen to our customers as they tell us their "challenges" and needs. Our customers are varied. Ranging from the patient or clinical care-giver to the purchasing agent or hospital executive. All have varying needs, yet all are important for us to understand and serve as well as we can.

**What in terms of cost-savings/benefits does your technology bring?**

Roche OMNI S blood gas analyzers offer many value-added services and benefits. From the maximum 42 day on-board stability of reagents to the 40 day supply of on-board quality control material and zero-maintenance electrodes, the analyzers' features reduce the time it takes to perform QC and to change reagent packs and maintain electrodes. These features also reduce the downtime required for the analyzer to calibrate and come back "online" after a reagent change. Roche offers Neonatal Bilirubin with results that are comparable to the laboratory standard. By offering this test near the NICU, you reduce the sample volume needed to obtain a result and shorten the time for reporting a result. Neonatal bilirubin results on the OMNI S blood gas analyzer, due to the sample being measured in the Co-Oximeter, can be performed without the need for additional reagents, thereby reducing the cost of reporting. Roche offers the only blood gas system with an FDA 510 (k)-cleared claim for the measurement of pH on pleural fluid. According to CAP and the American College of Chest Physicians, a blood gas analyzer is the method of choice for performing pH on pleural fluids. If a blood gas that is not FDA 510 (k)-cleared is used for measuring pH on Pleural Fluids, the test must be treated as a CLIA high complexity test. This requires much more quality and validation work and also requires that a laboratory-trained technician perform the testing. By using a Roche blood gas analyzer, the test is only a moderately complex test and may be performed by respiratory therapy and other technicians within the hospital. The costs saved by keeping tests to a moderately complex level may be significant, depending on the capability within the hospital. One of the most significant savings may be realized by performing "Glycemic Control" or acid base monitoring of patients in the ICU. Using the Roche OMNI S blood gas analyzer with Metabolite sensors, the ICU can now perform frequent blood glucose and/or lactate measurements on their patients. The Roche OMNI S analyzer onboard software provides patient trending and Acid Base Mapping. These two features help the clinical staff closely monitor the patient's acid-base balance as well as his or her glycemic control. There are many published studies that have documented significant clinical improvement as well as cost savings when a systematic process of glycemic control is practiced. By using the Roche OMNI S Blood Gas analyzer, patients connected to an arterial or venous line may have glucose and/or lactate samples taken without performing repeated finger-sticks.

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# Now you won't have to do backflips to meet regulatory compliance.

Why? Because the **cobas b** 221 blood gas analyzer:

- ☑ Is the only analyzer with FDA 510(k) clearance for pleural fluid pH testing
- ☑ Provides innovative and reliable IT solutions for remote control, patient data management and QC reporting
- ☑ Features an extensive, labor-saving AutoQC® module with automatic lot-to-lot comparisons
- ☑ Offers eQAP, online CEU programs and remote troubleshooting capability

**To find out more, contact your Roche Diagnostics representative or call 800-428-5076.**

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