bioMérieux CONNECTION

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Message from bioMérieux

Herb Steward
Executive Vice President and General Manager, bioMérieux North America

I'd like to welcome you to the second edition of bioMérieux's *Connection* newsletter for 2007. We are all immersed in a fast-paced, ever-changing healthcare environment and this newsletter is one way we plan to keep you up-to-date on new products, technology and company news.

On behalf of the executive team at bioMérieux, I am excited to share some information about key changes taking place in our organization. We are in the process of creating a more robust service, production and distribution organization, these changes will allow us to exceed current standards for superior service and product quality. The new structure will also help bioMérieux accelerate new product releases and bring you innovative technology to help your business grow.

Earlier this year, Stéphane Bancel, our new President and CEO announced our vision and 2007-2012 strategy.

bioMérieux plans to intensify its focus on specific areas, including microbiology, clinical solutions, molecular diagnostics, emergency medicine and industrial microbiology. Stéphane also announced the formation of a Theragnostics Business Unit based in Cambridge, MA. The Theragnostics group will partner with pharmaceutical and biotechnology companies to develop the role of diagnostic tests in Personalized Medicine and for product development. This strategy will also let bioMérieux expand its product lines in order to meet your changing needs and stay abreast of the emergence of new pathologies.

The new year is getting off to a good start. Thank you for your dedication and support, we appreciate your business and wish you a safe and successful year.

from diagnosis,
the seeds of better health

BIOMÉRIEUX

Zack Blair, QA Coordinator/Microbiologist
and Lisa Seaton, Perry County Memorial Hospital
Tell City, Indiana.

SECOND STOP: TELL CITY, IN

The VITEK® 2 Compact in Action. Part 2 of 3.

bioMérieux's VITEK 2 Compact automates bacterial identification and antibiotic susceptibility testing (ID/AST) in small to mid-sized microbiology labs, providing everything needed for testing in an easy-to-operate format.

We recently spoke with some users of the system to get their perspective on the VITEK 2 Compact in real-world settings. Last time, we headed to Fort Stewart, Georgia, to hear from Joe Laynor at Winn Army Community Hospital. Next time, we're bound for Tiffin, Ohio to meet Janet Lane, Microbiology Supervisor at Mercy Hospital.

This month, our travels take us Tell City, Indiana, where Zack Blair had a rare opportunity to build a microbiology lab from scratch.

Where No Micro Lab Had Gone Before.

We're a 55-bed facility, serving a rural community. Our goal in Microbiology Services is to provide information to the physician in a timely manner, using the best technology that's available and that's affordable for us.

When the hospital opened, it was cost effective to send everything to a reference laboratory. But it wasn't providing services for patients in a very timely manner. So we decided to open a microbiology lab here, just within the last year or so.

I was very involved in the process of evaluating the equipment and getting the lab set up. It was a huge project … I've come to discover that it's pretty rare to build a micro lab from scratch these days.

Selective Labs Choose VITEK.

When we were going through the selection process, we looked at all the different manufacturers and we compared everything. I've used other systems for microbiology, and personally I just like bioMérieux's products – especially the VITEK systems – over others that are available.

The things that weighed heavily in favor of the VITEK® 2 Compact were accuracy, reliability and speed of reporting. In the time it takes some systems to incubate, I can already have my results done with VITEK. Plus, there's an advantage with the efficiency of the cards – since there are no trays to set up, it's pretty hands-off and you don't have to manipulate it very much. It's really neat, really automated. We really liked the pre-barcoded test cards; that really helps in traceability of samples.

We didn't get a huge amount of space to set our stuff up in – that's not reality. We're a small microbiology department, and the size of the machine fits perfectly with our small lab.

After we chose the system, the installation process went smoothly. Markita Weaver, our Client Consultant, came in, talked to us about what we needed to have as far as samples and tests, and we did our correlations.

I personally went to training on the BacT/ALERT® we installed about the same time, and experienced the same thing – I got the BacT/ALERT plus OBSERVA®, I learned everything I needed to know and once I came back, I was ready. I learned how to train the staff, so I could back information to our techs. I also got that in-depth knowledge that I needed to act as a key operator for the machine.

We're very happy with the OBSERVA software. I used the VITEK 2 Legacy system, and I feel like OBSERVA is ten steps up. It's great for pulling reports. You can query or search any data that you really want to customize, and fit the specific needs for your lab.

And we utilize the AES a lot. With each organism that we put on the VITEK, it actually flags us with the Expert – letting us know whether we need to review or look at this a little bit differently. Plus, we like the fact that it crosschecks it with a phenotype database. There are more than two eyes looking at it; you've got, what is it, a greater than 100,000 reference database? It's a confidence factor.

In the time it takes some systems to incubate, I can already have my results done with VITEK.

Everything I Needed to Know I Learned in NC.

We sent a person to North Carolina for training on the VITEK system, and they came back and trained the rest of our staff on-site. Also, Markita came on site to help with the training, which eased that process quite a bit. She has been extremely helpful in answering questions, pretty much on demand – we'll just call her, she's very accessible and she gets back to us with the answer. We're very impressed.

We've had the Compact for more than six months now. It's too early for any hard numbers, but it's had a pretty immediate impact on patient care. Just for our urine cultures alone, whereas we were sending them out to reference laboratories we've improved the turnaround time by at least 24-36 hours – that's a definite change, and that was noticed immediately. We got quite a few positive responses from physicians and clinicians; that made us feel pretty good. ▮

[»] Next time: Tiffin, Ohio

NATIONAL MEDICAL LABORATORY WEEK

CELEBRATING "QUALITY CARE FROM QUALITY INDIVIDUALS"

bioMérieux would like to take this opportunity to send our gratitude and appreciation to the dedicated Medicinal Laboratory Professionals who make a difference each day in their communities throughout America.

Many times the "hidden heroes," we recognize that your efforts provide valuable information that impacts clinical decisions resulting in improved patient care.

In support of your service, and to assist with the challenge of keeping up with changing technology, bioMérieux's 2007 focus is on providing increased continuing education in the areas of Microbiology, Immunology and Molecular Biology. We will be providing continuing education in the form of webinars on the bioMérieux education website, mobile presentations offered on our Innovation in Motion Tour Bus and knowledge forums at major national meetings.

Again, we commend your hard work and thank you for your contributions. ▮

DIAGNOSTIC MARKERS:

Empowering Clinical Decisions in the Emergency Department PART 2

At the American College of Emergency Physicians (ACEP) 37th Annual Scientific Assembly in New Orleans, bioMérieux hosted a scientific symposium on Advancing ED Clinical Decisions with Diagnostic Markers. During this special event, two of the leading researchers in this area presented new findings and exciting clinical implications from their recent work.

The symposium was moderated by Dr. Jerald Solot, Chairman of Emergency Medicine at the University of Pittsburgh Medical Center Shadyside Hospital (UPMC-Shadyside).

In the last issue of Connection, we featured the presentation given by Dr. Philip Wells, detailing the use of D-dimer assays in the diagnosis of Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT).

This month, we're pleased to present some of the research of Dr. Beat Müller, Professor of Internal Medicine and Endocrinology, Head of the Endocrine Unit and Consultant for Internal Medicine at the University Hospitals of Basel, Switzerland.

Dr. Müller has attracted considerable research funding and overseas clinical and experimental research projects focusing on the role of hormones during illnesses, especially during inflammation and infections. He investigates the functional regulation and effects of calcitonin peptides, including procalcitonin, in systemic inflammation, bacterial infections and sepsis. Dr. Müller was the principal investigator of the first and third subsequent intervention studies, involving more than 1,200 patients, which examined the application of a sepsis biomarker as a guide to antibiotic use for suspected lower respiratory tract infections.

Procalcitonin: A Key Biomarker in the Diagnosis of Respiratory Infections.

The context for Dr. Müller's presentation is the overuse of antibiotics. Many people present to the ED or to their primary care physician with a fever, cough and chills. Such symptoms can be moderate and transient, or they can be signs of a serious infection.

Very often, these patients demand an antibiotic treatment. Unfortunately, the patients themselves have no idea whether they have bacterial infection – for which antibiotics are the appropriate treatment – or a viral infection, which doesn't require their use. And many physicians take the view that some patients will progress to sepsis, and they can't predict which, so it's better to start antibiotics early, just to be on the safe side.

The United States is among the world leaders in MRSA (methicillin resistant Staphylococcus aureus). 75% of the antibiotics prescribed are for the 75% of infections that are viral, leading to increases in resistance.

So Dr. Müller posed the question: *can a simple, reliable test be developed that will detect which type of infection a patient has?* His work with the hormone procalcitonin (PCT) as a marker for bacterial respiratory infections has shown very promising results – and highlights the very immediate and practical impact it can have.

Where PCT Comes From.

When a person is healthy, calcitonin, a hormone derived from PCT production, is produced in the thyroid. But when a person is infected, or that infection progresses to sepsis, their entire body effectively becomes an endocrine gland, and many systems in the body begin secreting PCT itself.

Initial study of the underlying reasons for this focused on the thyroid gland and fat cells. When infected, fat cells are surrounded by toxins and cytokines – the "cocktail" that induces production of calcitonin. However, fat cells (and most other cells throughout the body) don't have the same capability as the endocrine cells in the thyroid, and are unable to further process the PCT into calcitonin. As a result, PCT is directly secreted by these cells.

As the whole body starts making PCT, it isn't stored but released into the bloodstream. Levels of PCT found in the blood increase dramatically with the severity of bacterial infection.

Making its Mark in Respiratory Infections.

Dr. Müller hypothesized that PCT may be responsible for the toxicity of sepsis. Animal studies concluded that PCT has a probable role in infection, and that neutralizing it might save severely infected subjects.

The next step was applying this knowledge to the treatment of human beings, first in the ICU.

PEDCRIP, the observational study, examined the prognostic value of endocrine dysfunctions in critically ill patients with sepsis, most of whom had pneumonia, and measured their PCT levels. It found that the likelihood for bacterial infection increased with the elevation of PCT.

Studies Show: Reduced Antibiotic Use & Shorter Duration.

The next question to consider was how to use the knowledge gained from the observational study in a clinical setting. *Could it become part of clinical reasoning for individual patients?* What would the cut-off ranges need to be? Dr. Müller and his team hypothesized that if PCT levels were low, patients could be sent home without antibiotics.

He made it clear that there is never an either/or, "pathological" or "normal" test. In establishing the ranges for the ED studies, they determined the need for a highly sensitive test, and used lower cut-off numbers than those established in the ICU observational study to increase the safety margin.

Guidelines were set based on four specific ranges – 1) No antibiotics, 2) Maybe antibiotics, 3) Probably antibiotics, and 4) Definitely antibiotics – and a treatment protocol created. If the patient was not on antibiotics, follow up in 6-24 hours (analyzing on a range of factors); if the patient was on antibiotics, reevaluate at time points of 3, 5 and 7 days and determine the proper course.

In the first study, ProRESP, overall antibiotic use for lower respiratory tract infections was reduced from 83% of patients to 44%. More specifically, the prescription rates for patients with community-acquired pneumonia (CAP) were about the same in both the PCT patients and the [+]

(continued on page 6)

75% of the antibiotics prescribed are for the 75% of infections that are viral, leading to increases in resistance.

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[-] control group. But the rates for acute exacerbations of chronic bronchitis (AECB) were cut in about half, and those for asthma and bronchitis fell dramatically.

The next step was to determine the proper duration of antibiotic therapy – *10-14 days? 7-10 days? Something else?*

The 300 pneumonia patients in the ProCAP study had their PCT levels checked at 2, 4, 6 and 8 days. In the PCT monitored group, only 50% of the patients were treated with antibiotics for more than 4 days, and only 30% more than 6 days. Overall, the mean duration of antibiotic treatment in the PCT group was less than half – 6 days – versus 12.9 days for the control group.

The PCT group had demonstrably fewer antibiotic side effects.

Müller also laid out clear guidelines for using PCT in general practice:

- **Use it to get experience.** Learn what the cut-off range is in your specific setting.
- **Use it cautiously, like any marker.** The sicker the patient, the more cautious you should be.
- **Use it selectively.** Only after a thorough history and examination, and with a focused hypothesis and strategy in mind.
- **Use it wisely.** If a patient is admitted in shock – Initiate antibiotics stat!
- **Conduct studies,** report your results, and discuss the positives and negatives.

Enhancing the Use of Treatment Guidelines.

Dr. Müller went on to explore how these results could be adapted for us as guidelines in individual patients.

For example, one of the standard treatment guidelines indicates that the duration of antibiotic use is determined by presence of the pathogen. Normally, however, there's no clear distinction between patients with a positive blood culture and those with a negative result for a pathogen – meaning that clinicians don't use a negative result to determine the duration of treatment. But monitoring with PCT provides a much more clear, quantitative distinction among patients than merely identifying those with positive and those with negative blood cultures, resulting in it being a much more actionable guide to appropriate treatment.

Another guideline indicates that antibiotic duration should correlate to CAP severity, based on the PSI (Pneumonia Severity of Illness) score. In this case as well, there's normally no clinical difference in duration of antibiotic treatment between patients with a PSI of 1-3 and those with a PSI of 4-5. The PCT monitored patients in each category, though, showed a clear difference – and the PCT group had shorter durations overall, especially those with PSI scores of 1-3.

Safe Over the Long Term.

As with the recalibration from the ICU to the ED, the use of PCT as a biomarker needed to be adapted to the primary care setting, taking co-morbidities into account and once again adjusting the cut-off levels.

In the third study, ProCOLD, more than 200 patients were evaluated against the Kaplan-Meier estimate of the probability of remaining relapse-free and alive at six months. 40% of the PCT group received antibiotics on admission, compared to 72% of the control group. Even with this variance, there was no difference in recurrence rates: Using fewer antibiotics does not mean patients will get sick more often.

And Effective Against Over-Prescription.

Müller drew attention to the fact that, by country, a high use of antibiotics correlates to high resistance – mainly because of antibiotic use in the primary care setting.

His next study explored using PCT as a tool to convince doctors and patients not to overuse antibiotics – or, put another way, to counteract the "give me antibiotics or I'll sue you" phenomenon.

The ProDOC/PARTI outcomes study looked at whether using PCT guidance would cause patients to be sick longer. One endpoint measured was the number of sick days taken; there was no difference between the PCT group and control group, indicating that the PCT group was not getting sicker. In addition, the PCT group had demonstrably fewer antibiotic side effects – something that physicians will want to let their patients know.

The other endpoint measured was overall antibiotic use. In the PCT group, both the number of prescriptions and the duration decreased by almost 80% as compared to the control group. And Müller noted that this study was conducted in Switzerland, a country with very low prescription rates to begin with. He estimated that this 80% reduction would correlate to almost 95% in the U.S.

Putting PCT to Good Use.

In summary, Müller said that these four intervention studies have shown that use of PCT as a biomarker works. It has the potential to cut the use of antibiotics in half, and shorten the duration, in both ED and primary care settings. ▮

New Developments in Automated Nucleic Acid Extraction

Deliver Quality Results and Improve Productivity in the Molecular Diagnostic Laboratory

Steve Shumoski, Clinical Marketing Manager, Molecular Systems, bioMérieux, Inc.

Molecular biologists in clinical laboratories are faced with the challenges of nucleic acid testing every day. One of the more demanding areas is the extraction of nucleic acid from biological samples. Indeed, sample preparation is considered by many to be the most painstaking area of molecular-based testing with laboratories indicating they expend a significant amount of their labor resources in this area. As the typical starting point for molecular diagnostics, it is where efficient extraction of nucleic acid and removal of potential downstream reaction inhibitors often impact the end result. The starting materials themselves can be fairly demanding when there are various volumes and/or types of samples depending upon the test requirements. Infectious disease applications are particularly critical since there may be relatively little target nucleic acid for recovery and concentration in the final eluate.

NucliSENS™ easyMAG

There is a wide variety of manual and automated methods for extracting nucleic acid in the clinical laboratory. Manual methods have certainly come a long way over time with various commercial offerings that include complete kits containing most of the components needed to isolate nucleic acid. However, most manual methods are still fairly labor intensive and are limited in terms of overall throughput. Automated systems designed for medium to large laboratories have grown in presence over recent years and while they have certainly improved upon throughput, they generally have disadvantages surrounding complexities of the robotics, overall lack of flexibility, and the fact that some require a large amount of disposable materials.

bioMérieux recently developed the NucliSens® easyMAG™, an automated system specifically optimized for extracting high-quality RNA and DNA in a very user-friendly manner. The focus of the development was two-fold: to maximize the performance of the underlying nucleic acid extraction chemistry, and to enhance the overall design, accessibility and convenience of an automated platform particularly when compared to earlier generation instruments. ▮

[] To read the complete article on the NucliSens® easyMAG™, go to www.biomerieux-usa.com/connection

ASM EVENTS:

Customer Appreciation Party Tuesday, May 22
7:00pm - 11:00pm; Location: to be announced

Customer Panel Symposium: Interactive User Group Session with Corporate R&D executives and the ID/AST Program Director.
Wednesday, May 23; Location: to be announced

5:00pm Registration and Hors d'oeuvres
6:00pm Herb Steward, Executive VP & GM for bioMérieux, North America
6:15pm ID/AST Interactive User Group Session: Michel Peyret, Corp R&D Executive
7:00pm Customer Panel Discussion: Lab's Impact on Reducing HAIs and Curbing Emerging Resistance
8:15pm Cocktail Reception

Please submit questions for our Interactive ID/AST user group at our ASM web site www.biomerieux-usa.com/asm2007. This site also provides constant updates on our activities at ASM 2007.

We look forward to seeing you in Toronto!

2007
SHOWS AND CONFERENCES

Society for Healthcare Epidemiology of America (SHEA)
Baltimore, MD • Apr. 14-17

Clinical Virology Symposium
Clearwater Beach, FL • Apr. 27-28

National Patient Safety Foundation (NPSF)
Washington, DC • May 2-4

American Society of Microbiology (ASM)
Toronto, Canada • May 21-25 – *Booth #709*

Save the Date:
Tuesday, May 22, 2007
Annual Customer Appreciation Event
Wednesday, May 23, 2007
Customer Panel Symposium

Association for Professionals in Infection Control (APIC)
San Jose, CA • June 24-28

American Society of Health-System Pharmacists (ASHP)
San Francisco, CA • June 25-27 – *Booth #229*

American Association for Clinical Chemistry (AACC)
San Diego, CA • July 15-19

Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
Chicago, IL • Sept. 17-20

Infectious Disease Society of America (IDSA)
San Diego, CA • Oct. 4-7

American College of Emergency Physicians (ACEP)
Seattle, WA • Oct. 8-11

Association of Molecular Pathology (AMP)
Los Angeles, CA • Nov. 7-10

American Society of Health-System Pharmacists (ASHP)
Las Vegas, NV • Dec. 2-6 – *Booth #3217*

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Please share your comments and suggestions with us through your local account manager or by emailing us at the address above. As always, we thank you for being a bioMérieux customer.