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bioMérieux Connection

In this issue:

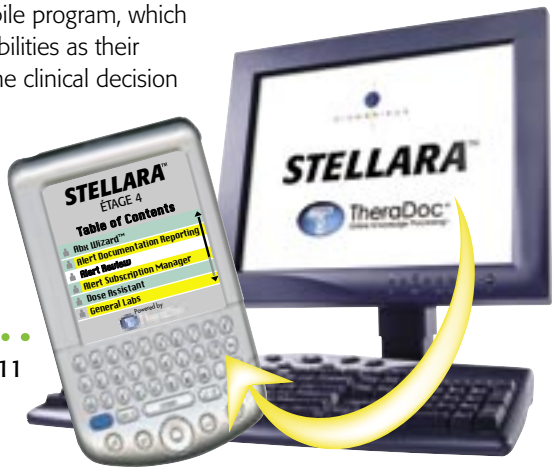
STELLARA™ available January 2005!

bioMérieux is pleased to launch STELLARA™, the comprehensive new suite of real-time, clinical-intervention software systems that we previewed to you in last month's newsletter.

STELLARA brings the microbiology results (ID/AST) from bioMéreiux's leading BacT/ALERT® and VITEK® systems directly to the pharmacist and clinician — in real time — to support quicker actionable results.

STELLARA is an important advancement in integrated technology for infectious disease intervention. In the last newsletter, bioMérieux gave you a brief overview. Now we would like to show you some of the features of the four different étages of STELLARA. Advantages of STELLARA include the modular, scalable and mobile program, which allows institutions to add more features and capabilities as their needs grow. Another advantage is the power in the clinical decision support data base for infectious diseases.

Here are some of the highlights of the four étages. Your local bioMérieux account manager will be happy to explain them in greater detail and give you a demonstration. In addition, please visit www.biomerieux-usa.com/stellara



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DAVINCI® Immunoassay Analyzer

Load samples. Load reagents. Press "Start." Walk away!

Now busy laboratories can streamline high-volume immunoassay testing with bioMérieux's space-saving new analyzer — the DAVINCI®. This fully integrated, flexible system improves workflow efficiency and reduces hands-on time while giving laboratories total in-process control, for repeatable, reliable results.

High capacity throughput is so easy!

DAVINCI handles a large, 15-microplate workload smoothly and easily, thanks to software-guided, random-access plate loading and unloading. Its innovative XYZ random microplate transportation provides fully independent multi-tasking operation of all instrument modules. Four independent sampling channels handle up to 192 bar-coded primary samples, 16 calibrators, controls, and 6 sample diluents.

DAVINCI Immunoassay Analyzer continued on page 2

BIOMÉRIEUX

from diagnosis,
the seeds of better health

API® Voice Response System is going away December 17!

If you have not yet recived your free APIweb™ CD, order your electronic code book access now! The API® Voice Response System and code books will no longer be available after December 17. They have been replaced by the new APIweb electronic code book, which allows instant interpretation of API strip results via the Internet or a CD.

APIweb has the databases for all your API strips, and updates to databases on the Internet version will be made periodically at no charge.

To order your free APIweb, just let a customer service representative know which version of APIweb you prefer – Internet (Product Number 40011) or CD (Product Number 40012).

Get your updated list of VITEK® 1 and VITEK® 2 cards

They're hot off the press — flyers listing all current VITEK® 1 AND VITEK® 2 antibiotic susceptibility test card configurations.

Ask your local account manager for a copy for your laboratory, or email the *bioMérieux Connection* newsletter at biomerieux.connection@na.biomerieux.com. Whenever we update the cards with new antibiotics, we'll also update these handy flyers and notify you through the newsletter. Plus, we will post these card configurations on our website in the VITEK 1 and VITEK 2 "Test Card Configurations" sections.

DAVINCI Immunoassay Analyzer
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DAVINCI's easy-to-use LED system guides all sample, reagent (up to 25 containers), and pipette-tip loading processes. Fully independent pipetting modules keep samples and reagent pipetting steps separate, which eliminates cross-contamination and provides maximum safety, speed, and reliability.

Create your own protocols

DAVINCI is a flexible, open system that offers laboratories the freedom to develop their own protocols for the assay being performed.

Identification and verification at every step — a DAVINCI stronghold!

With the DAVINCI analyzer, you can have the confidence that your processes are identified and verified at every step. All microplates, reagents, samples and sample loading positions are bar-coded for identification and verified during each transportation step for maximum security.

If you would like to learn more about how DAVINCI can improve the workflow efficiency in your immunoassay laboratory, contact your local account representative.

Ergonomic study reveals VITEK® 2 causes significantly less upper-extremity strain than other system

bioMérieux is pleased to release the findings of a technical ergonomic analysis that shows its VITEK® 2 automated bacterial identification and antibiotic susceptibility testing (ID/AST) system causes significantly less strain than another manufacturer's automated ID/AST system.

The ergonomic study was performed by Worksite International, Inc. and commissioned by a customer of bioMérieux's VITEK 2 system. Worksite International utilizes a Strain Index[1] (SI) method to evaluate the level of risk for developing a disorder of the hand, wrist, forearm or elbow from a certain job. According to the Worksite study, the SI score for bioMérieux's VITEK 2 Clinical Laboratory Scientist (CLS) work cycle over 2-4 hours was 6.75, the lower the number being the more ideal. The closest competitor on an identical CLS work cycle over 2-4 hours had a strain index of 60.75.

The study compared — through task and ergonomic analysis — the biomechanical advantages and disadvantages of the card set-up process of the VITEK 2 ID/AST testing system with the other manufacturer's automated ID/AST system. The assessment included an analysis of workflow, work routines and work practices for the purpose of establishing best practices. The study was commissioned to help laboratories better understand the risks and exposures associated with performing automated ID/AST testing and the likelihood of developing a musculoskeletal disorder (MSD) to the upper extremities.

MSDs affect job performance across industries in an adverse way and result in lost work time and productivity. In the Bureau of Labor Statistics' 2002[2] report, which is the most recent to date, MSDs accounted for 34%, or almost 500,000, of the injuries and illnesses that required days away from work. Carpal Tunnel Syndrome sufferers missed an average of 30 days because of pain associated with repetitive tasks. In addition, wrist and shoulder injuries accounted for the longest average absence from work, 15 days.

To perform the study, a Worksite International ergonomist observed and videotaped the card set-up processes of both the VITEK 2 and the other instrument and performed time and motion (MTM) analysis of the essential work cycles. The data that was collected was then validated by using the Strain Index, a proposed method to analyze jobs for risk of distal upper extremity disorders to determine the relative Strain Index of the VITEK 2 card set-up process compared to the same process of the other system.

About the Strain Index

A validated tool developed by Steven Moore, Medical College of Wisconsin and Arun Garg, University of Wisconsin, the Strain Index is used to evaluate the level of risk for developing a disorder of the hand, wrist, forearm, or elbow from a certain job or task. The Strain Index is an appropriate tool to use when attempting to evaluate the risk of developing an MSD in a hand-intensive task.

About Worksite International, Inc.

Worksite International, Inc. located in Monterey, California, has been an established consulting company since 1993. The company provides office and technical ergonomic analysis and training to business and industry for the purpose of injury prevention and management as well as for improving employee productivity and comfort. Worksite International offers custom ergonomics and workers' compensation program development and management, ergonomic analysis and training for the biotech industry as well as for other industries. The services emphasize the integration of quality health and safety work processes into the organizational culture. Alison Heller-Ono CMC, Certified Industrial Ergonomist and President/CEO of Worksite International conducted the ergonomic study comparing the two ID/AST test kit set-up processes.

1. Moore, S. and Garg, A., "The Strain Index: A proposed method to analyze jobs for risk of distal upper extremity disorders," American Industrial Hygiene Assoc. Journal, 56:443-458, 1995.

2. Bureau of Labor Statistics, Work Injury and Illness Rates, 2002.

Discontinuation of various VITEK® 1 gram negative cards

bioMérieux is committed to providing laboratories with VITEK® antibiotic susceptibility test card configurations that best reflect antibiotic usage within their institutions and that correlate with NCCLS guidelines. As new antibiotics are introduced and usage patterns change, there will always be a need to create new card configurations to replace outdated ones. As a result, we have brought you a number of new card configurations over the last year.

We have also planned a discontinuation of some of the older VITEK 1 cards, a move that we announced in a customer letter in December 2003. The announcement indicated that we would discontinue the cards on March 31, 2004. However, based on your feedback, we have postponed the discontinuation until May 31, 2005.

The reasons for discontinuing the cards include:

- Incorporating new antibiotics on cards
- Adding an ESßL confirmatory test on the majority of VITEK 1 gram negative cards
- Eliminating duplication of antibiotics within the same class on the same card
- Discontinuing cards that contain antibiotics that are no longer used in the U.S.

Product Number	Discontinued Gram Negative Card
V4518	GNS-108
V4519	GNS-109
V4520	GNS-110
V4521	GNS-111
V4522	GNS-112
V4523	GNS-113
V4524	GNS-114
V4528	GNS-115
V4271	GNS-118
V4332	GNS-120
V4355	GNS-123
V4356	GNS-124
V4357	GNS-125
V4358	GNS-126
V4525	GNS-203

Please note that we are not discontinuing any VITEK 1 Gram negative cards not listed in the above chart or Gram positive cards at this time. The GPS-105, GPS-106, GPS-107, GPS-108, GPS-109, GPS-110, GPS-111, and GPS-112 are still available.

bioMérieux at IDSA: "Rapidly Close the Circle of Care"

bioMérieux's exhibit booth theme at the 2004 Infectious Diseases Society of America (IDSA) annual meeting was "Rapidly Close the Circle of Care." For both clinical and economic reasons, today's circle of patient care must consist of integrated solutions. The challenge presented by infectious disease demands technology that recognizes sepsis, identifies bacteria, determines susceptibility and helps bring about the best possible outcome.

For two years, bioMérieux has sponsored Knowledge Forums in our booth, with speakers and topics that have immediate impact on infectious disease laboratories. During the bioMérieux Forums, the economic and clinical aspects of integrated solutions to infectious disease diagnosis and treatment were addressed. This year the speakers and topics were:

IDSA 2004 Boston

Dr. David Classen, VP, First Consulting Group, Salt Lake City, UT: "Pay for Performance: Surviving the New No Outcome – No Income World"

Dr. Joan Barenfanger and Dr. Donald Graham, Springfield Memorial Hospital, Springfield, IL: "Can ID Physicians Improve Outcomes by Influencing Lab Practices?"

24-Hour subculturing of positive blood cultures leads to faster ID/AST results

Blood cultures are considered to be one of the most important specimens processed by a microbiology laboratory. Prompt detection and reporting of positives is of critical importance. Cases of bloodstream infection (BSI) are often linked to underlying diseases and/or surgical procedures performed while a patient is in the hospital. Each year more than 750,000 people in the U.S. develop severe sepsis, and more than 215,000 die from the condition.[1] Mortality rates can be as high as 28-50%.[2]

Rapid turn around time for blood cultures and for identification and susceptibility (ID/AST) results can affect patient outcomes as well as impact the hospital's financial outcome. Several studies suggest that continuous-monitoring blood culture instruments may significantly reduce the time to notification of BSI.[3] This can also reduce the time required to obtain a result for an ID/AST on isolates recovered from septic patients.

How workflow affects reporting

Many laboratories monitor their blood culture instrument only on the day shift, generally from 7 a.m. until late afternoon. In studies performed by bioMérieux, it has been shown that monitoring blood cultures 24 hours a day can have a significant impact on the turn around time for ID/AST results from VITEK® 1/VITEK® 2 systems. In fact, these studies demonstrated that by having technologists available around-the-clock to subculture positive blood culture bottles, 64% of patients with septicemia could have their VITEK 1/VITEK 2 ID/AST results on the chart 24 hours sooner. This translates into cost savings for the hospital by changing to a more targeted and cost-effective therapy, reducing the number of diagnostic procedures and reducing the patient's length of stay (LOS), while improving overall patient care.

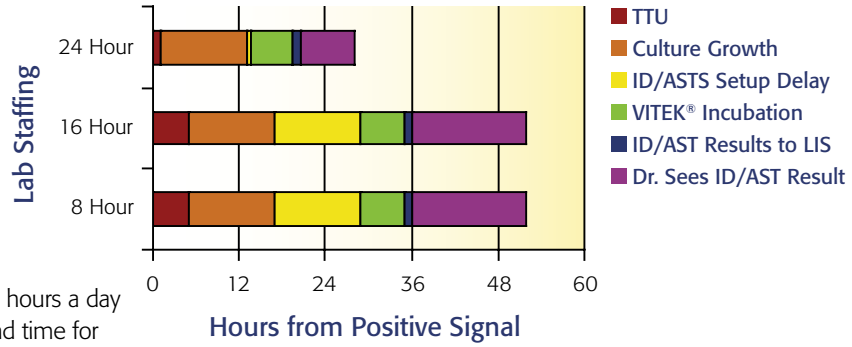
For instance, based on a $1750-per-patient cost savings, as demonstrated by Dr. Joan Barenfanger,[4] an institution could realize an annual savings of over $400,000. This figure assumes a bottle volume of 36,000 per year and a 10% positivity rate.

Around-the-clock reporting

The BacT/ALERT® 3D is an easy-to-use microbial detection system that can be placed in areas in the laboratory that allow technologists to hear the positive-bottle signal 24 hours a day. Positive blood culture bottles that are subcultured as soon as they become positive significantly reduce the turn around time for blood culture ID/AST results, which can lead to improved patient care and better hospital financial outcomes.

In the next issue of *bioMérieux Connection*, we will show you how your BacT/ALERT® 3D system can have a positive impact on Diagnosis Related Group (DRG) reimbursement.

ID/AST TAT impact — 3rd shift +BC



24-hour faster ID/AST

Turn-Around-Time (TAT) for 24-hour laboratory coverage versus 16-hour or 8-hour coverage when blood culture turns positive on third (overnight) shift.

Lab subcultures positive blood cultures (+BC) on two or more shifts

Sets per year	18,000
Positive rate	10%
Average number bottles per patient	5
Number of patients w/ +BC per year	360
AST results 24 hours sooner for 64% of patients with +BC	230
LOS/COS savings per patient[2]	$1,750
LOS/COS savings per year	$402,500

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bioMérieux at ACEP

The American College of Emergency Physicians celebrated 25 years of emergency medicine as a specialty this year. ACEP reported that over 114 million people seek care in the nation's emergency departments annually. At the Scientific Assembly, held in San Francisco in October, bioMérieux joined more than 300 health-care industry suppliers to greet 5,700 emergency department attendees with new diagnostic products and solutions for their patient-care needs.

Scientific Assembly
San Francisco

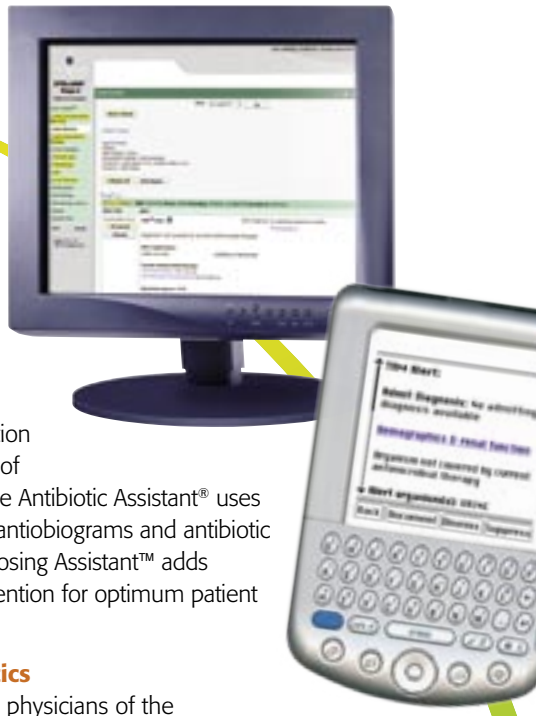
bioMérieux hopes your emergency physicians share the diagnostic educational information that they learned with you, their friends in the laboratory. Here is a small recap of what we demonstrated in our exhibit booth.

VIDAS® D-Dimer Exclusion™

Busy emergency physicians learned that there is a lot of difference in D-dimers when it comes to safe and accurate exclusion of deep vein thrombosis (DVT) and and pulmonary embolism (PE) as a diagnosis in low- to-moderate-probability outpatients. VIDAS D-Dimer Exclusion, a rapid ELISA assay, has sensitivities and negative predictive values (NPV) greater than 99%* and provides results in under an hour. Laboratories will be glad to know that the assay is cleared by the U.S. Food and Drug Administration (FDA) to exclude both DVT and PE in conjunction with only a pre-test probability assessment in outpatients. Ask your ED physicians if they brought you any information on VIDAS D-Dimer Exclusion, the Gold Standard.

STELLARA™

bioMérieux debuted the STELLARA point-of-care PDA clinical decision support system to provide emergency physicians with a knowledge-enriched database for confirmation and recommendation of anitbiotic therapies. The Antibiotic Assistant® uses your institution's own antiobiograms and antibiotic formulary, while the Dosing Assistant™ adds timely antibiotic intervention for optimum patient therapies.



Molecular Diagnostics

We also reminded ED physicians of the advantages of asking their laboratories for more diagnostic results via molecular methods such as bioMérieux's NASBA technology. We also provided them with information about the Medsite® Grand Rounds™ educational course (free C.M.E.) on aseptic meningitis that we showed our readers in an earlier issue of the *bioMérieux Connection*. That site is: www.medsite.com.

*Perrier A, et al. The Lancet 1999, 353; 190-195.

VIDAS® D-Dimer Exclusion™ receives Clinical Diagnostics Product Innovation of the Year award

The Frost & Sullivan Award for Product Innovation of the Year is presented each year to the company that has demonstrated excellence in new products and technologies within their industry. Frost & Sullivan recognizes companies that have shown innovation with a novel product that has had a profound impact on the industry.

bioMérieux is proud to be this year's recipient of the "Clinical Diagnostics Product Innovation of the Year Award" for VIDAS® D-Dimer Exclusion.™ This award is bestowed on the company that successfully develops a product that is believed to provide a unique set of benefits over existing products on the market.

VIDAS D-Dimer Exclusion is the only rapid Enzyme Linked Immunosorbant Assay (ELISA) cleared by the FDA to exclude a diagnosis of both deep vein thrombosis (DVT) and pulmonary embolism (PE) in outpatients, with only a pre-test probability assessment and no further testing.

bioMérieux Connection is now on the web

Lose your *bioMérieux Connection* newsletter? Don't worry, you can always download it from bioMérieux's website at www.biomerieux-usa.com. We post all issues of the newsletter there for your convenience.

Not all d-dimer assays are created equal and neither are their units!

The most recent CAP Survey sample for D-dimer prompted several calls to bioMérieux's hotline to assist customers in determining in what units their assay was reported and what the difference was between the units. Standardization of D-dimer reporting is an enigma. We will make an attempt to explain the mystery here.

Digestion of fibrin clots by plasmin produces a heterogeneous population of fibrin degradation products (FDPs) of varying molecular weights containing variable numbers of D-dimer domains. Each manufacturer's assay exploits the specificity, binding capacity and reaction kinetics of its selected monoclonal antibody for specific D-dimer epitopes. Variations in overall immunogenicity of the antibodies and the robustness of the test methods result in differences in clinical specificity, sensitivity and Negative Predictive Value. In addition, each assay uses its own preparation of calibrators that, together with variations in the antibodies, make it virtually impossible to "harmonize" or "standardize" quantitative results between manufacturers' assays.

The type of calibrator provided with a D-dimer assay kit dictates the reporting units. Manufacturers may choose to provide calibrators that are based upon preparations of either purified D-dimer complexes or from

FEU ng/ml

whole blood clot lysate. The latter, and most common preparation, mimics the physiological formation and lysis of a clot in an *in vitro* system. Therefore, selection of a calibrator influences the quantitative interpretation of the immunoreactivity of the monoclonal antibody, thereby introducing a third variation between assays. Final D-dimer assay results are usually reported in ng/ml or µg/ml, based on comparison of the immunological response of the patient's sample to the immunological response of known concentrations of D-dimer in the calibrator.

If the calibrator is prepared from purified D-dimer complexes, the result will be reported as "ng/ml or µg/ml." If the calibrator is prepared from a whole blood clot lysate, results will be reported in (fibrinogen equivalent units) FEU ng/ml or FEU µg/ml. This is because when the lysate is prepared, the fibrinogen in the plasma is completely converted to cross-linked fibrin and is subsequently completely lysed. Therefore, by definition, the total mass of FDPs in the lysate is equal to the starting amount of fibrinogen. For example, if the starting plasma source has a fibrinogen level of 3 mg/ml (determined by standard gravimetric methods), the concentration of FDPs in the final lysate is 3 FEU mg/ml. The lysate is then further diluted and supplied as a calibrator with a specified concentration (e.g, 4 FEU µg/ml). The actual immunoreactivity of a purified D-dimer can be estimated by dividing the FEU result by a factor of two.

Both of bioMerieux's D-dimer assays — VIDAS® D-Dimer Exclusion™ and MDA® D-Dimer — report results in FEUs per ml. There has been some confusion regarding reporting units on VIDAS D-Dimer Exclusion because the FEU designation does not appear on the result tape. Rest assured that the reported result is FEU ng/ml, is not converted by the instrument and is consistent with published cutoffs and units reported in peer-reviewed publications. Please carefully review your package insert for result reporting information.

Written by Wim PM Houdijk, PhD, Scientific Officer, Hemostasis, Global Research and Development, bioMérieux BV, and reprinted by permission of www.CLOT-ED.com.

bioMérieux welcomes a new manager of clinical and scientific affairs

Dr. Jane Hata, PhD, has joined bioMérieux as senior manager of medical and scientific affairs, where she provides technical, scientific and medical support for our U.S. commercial operations. Dr. Hata also serves as a liaison between bioMérieux and outside strategic investigators, physicians and consultants, and manages the activities of bioMérieux's customer-response laboratory.

Prior to her position at bioMérieux, Dr. Hata was a graduate assistant in the department of pathology at the University of Missouri's Columbia School of Medicine, where she also previously served as a senior research specialist. Dr. Hata completed a post-doctoral fellowship in clinical microbiology at the Mayo Clinic in Rochester, Minnesota.

A frequent presenter at national and international meetings for organizations, including the American Society for Microbiology, the International Society for Human and Animal Mycology and the University of Missouri-Columbia School of Medicine, Dr. Hata has also co-authored many articles in professional journals.

Dr. Hata is a member of a number of professional organizations, including the American Society for Microbiology, the Medical Mycology Society of the Americas and the Mayo Clinic Fellow's Association.

The Biphasic aPTT Clot Waveform
Identification and Clinical Implications

Clot Waveform Analysis

The bioMérieux MDA® System is a fully automated random-access hemostasis analyzer capable of performing clotting, chromogenic and latex-based immunoassays. Reactions are continuously measured by an advanced photo-optical system, and a visual display of the reaction profile is provided. For clotting assays, this optical profile is called a waveform because of its characteristic shape.

The clot waveform is mathematically processed by a software algorithm to derive the desired endpoint (i.e., the clotting time expressed in seconds). However, the waveform provides more than clotting time alone, and additional information on the dynamics of clot formation may be extracted from optical profiles that are generated when routine coagulation tests such as the prothrombin time (PT) and the activated partial thromboplastin time (aPTT), are performed.[1] An existing well-known application is the determination of the fibrinogen content from the total change in light transmittance observed in the PT test.[2] Furthermore, it has been demonstrated that clot waveforms show a different pattern in certain clinical conditions compared to normal. Examples include the presence of heparin,[3] disseminated intravascular coagulation (DIC),[4] antiphospholipid antibodies[5] and factor deficiencies.[6, 7]

To allow the identification and classification of abnormal waveforms, a set of mathematical parameters has been developed to describe the characteristics of PT and aPTT clot waveform profiles.[1] This patented Waveform Analysis technology[8] is based on first and second derivatives of light transmittance signals obtained during the coagulation reaction. On the MDA System this opens the possibility of automatically alerting the user that the sample exhibits an abnormal waveform response. The first available application is the A2 Flag™ which signals the presence of an atypical biphasic aPTT waveform.

MDA® A2 Flag™

1 Operational aspects: a simple, rapid and cost-efficient test

The A2 Flag is an indicator that an abnormal biphasic waveform (BPW) has been identified upon performing a routine aPTT test on the MDA analyzer. The BPW is characterized by an early drop in light transmittance before the actual formation of the clot. On the MDA, the change in light transmittance in the pre-coagulation phase is quantified by the slope_1 parameter (%T/sec; see figure). The A2 Flag is automatically recorded when the value of slope_1 exceeds a pre-set threshold limit that is user-definable. Moreover, the actual slope_1 value can also be reported, which will be useful in patient monitoring.

2 Mechanism and pathophysiology: LC-CRP, a novel marker of the acute phase response in critically ill patients

The early drop in light transmittance before the formation of the clot is the consequence of the formation of a Ca^{2+}-dependent complex of C-reactive protein (CRP) and lipoproteins, very-low-density lipoprotein (VLDL), in particular.[9] This lipoprotein-complexed CRP has been designated LC-CRP.

Highly elevated CRP is a prerequisite for the formation of this complex, and plasma samples that exhibit the BPW typically have CRP levels above 75 mg/dL. Therefore, LC-CRP and the BPW are a reflection of the acute phase response occurring in critically ill patients with inflammatory conditions. Not every plasma sample with elevated CRP, however, shows the BPW. At high CRP levels, the formation of the complex is critically dependent on lipoprotein levels. The latter are depressed during the acute phase response. In other words, the appearance of the BPW is the net effect of two opposing acute phase reactions: (a) a rise in CRP and (b) a fall in lipoproteins. The BPW, therefore, is not a surrogate marker for CRP and is a stronger predictor of clinical outcome than CRP or lipoproteins alone.[9, 10]

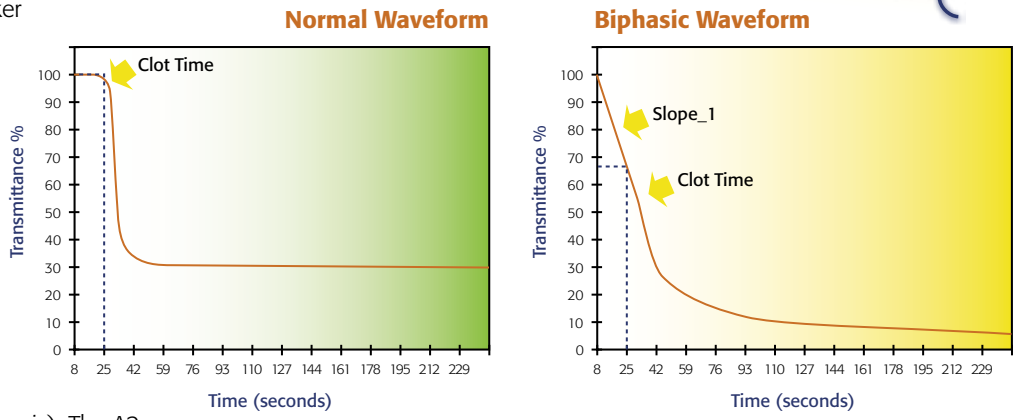
There are indications that LC-CRP also exists *in vivo*[11] and may play a pathogenetic role. The latter is illustrated by the observation that the VLDL fraction from plasma with the BPW has enhanced procoagulant activity.[12]

3 Clinical associations in critically ill: a prognostic marker for DIC, sepsis and survival

The BPW is highly prevalent in critically ill patients admitted to an emergency department (ED)[13] or intensive care unit (ICU).[9, 10, 14] There is evidence that the appearance of the BPW is an early marker of a hypercoagulable state, predictive for DIC.[9, 14, 15] Furthermore, the BPW is associated with sepsis,[10, 14] the most common cause of DIC. Finally, the BPW is associated with clinical outcome. It is a predictor of mortality[10, 14, 15] and the severity of the BPW, quantified by slope_1, shows real-time correlation with clinical progression (deterioration or resolution).[16] In non-ICU patients, the presence of the BPW is significantly associated with more adverse clinical events.[13]

Pearls for Practice

- LC-CRP, reflected by the atypical biphasic aPTT waveform, is a novel unique marker of the acute phase response.
- Detection and quantification of the biphasic response (A2 Flag, slope_1) is rapid, automated, robust and easy to perform because it is an adjunct to the routine aPTT test on the MDA system.
- The biphasic waveform (A2 Flag) is highly prevalent in critically ill patients and is a strong predictor of mortality and morbidity (DIC, sepsis). The A2 Flag may occur in conditions where overt DIC and/or sepsis are already documented by clinical and laboratory evidence, but also frequently precedes the final diagnosis of these conditions.
- In the ED/ICU setting, aPTT waveform analysis has the potential to augment current approaches to the diagnosis of DIC and frequently underlying conditions such as sepsis. It may be particularly useful in providing early warning of unsuspected developing DIC or sepsis. This may have a role in guiding and monitoring appropriate therapeutic intervention.



Normal and biphasic aPTT clot waveforms

A typical normal waveform is shown in the left panel. Characteristic of the abnormal biphasic waveform (right panel) is the early drop in light transmittance in the pre-coagulation phase; i.e. before the actual formation of the clot. The severity of the biphasic response is quantified by slope_1. This parameter (%T/sec) is the slope of a linear regression line forced through the optical signal changes recorded in the pre-coagulation phase. In a normal aPTT waveform, light transmittance is still 100% at 25 seconds, whereas this has dropped to below 70% at this time point in the severe biphasic response shown here (slope_1 = -1.76 %T/sec; typical lower 3SD-limit of a normal range distribution is –0.10 %T/sec).

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MDA A2 Flag Intended Use (cleared by the US FDA):
The MDA A2 Flag, in conjunction with a patient's aPTT test, is an indicator that an abnormal waveform pattern has been identified which may be associated with a developing or clinically evident coagulopathy, such as seen in sepsis or DIC. Additional diagnostic investigation is suggested.

Introducing Vironostika® HIV-1 Plus O

The new Vironostika® HIV-1 Plus O Microelisa System provides qualitative detection of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1), including Group O, in human specimens collected as serum, plasma or dried blood spots, as an aid in the diagnosis of infection with HIV-1. The Vironostika HIV-1 Plus O Microelisa System is the first Group O-sensitive test to receive FDA premarket approval.

The FDA asked diagnostic test manufacturers to improve detection of HIV-1 Group O in 1996, following confirmation of the first case in the U.S.* The individual with HIV-1 Group O initially presented for treatment in 1994, but conflicting results from diagnostic assays available at the time prevented immediate confirmation.

The Vironostika HIV-1 Plus O test detects antibodies to HIV-1 Group O as well as the more common Group M virus. The test performed during the clinical trials showed a sensitivity of 100% (95% confidence interval: 99.94% - 100%) and a specificity of 100% (95% confidence interval: 99.94% - 100%) in low-risk populations. Featuring a user-friendly design with color-coded, liquid, ready-to-use reagents, the assay is suitable for automation using 8-well strips, a 10µl sample input and a convenient 60-60-10 incubation format.

*Identification of HIV-1 Group O Infection – Los Angeles County, California, 1996. CDC MMWR July 05, 1996/45 (26); 561-565.

STELLARA™ Available January 2005! continued from page 1

STELLARA Étage 1

- Stand-alone PDA application for confirmation and recommendations of antibiotic therapies
- The Antibiotic Assistant®, an infectious disease knowledge database (with decision logic and references), uses your institution's antibiograms and antibiotic formulary
- The Dosing Assistant™ uses your formulary and works with The Antibiotic Assistant to provide timely antibiotic intervention
- Therapy intervention documentation printed to a local printer with infrared printer capability

STELLARA Étage 2

- 4 automated antimicrobiol alerts
  - resistant isolate
  - no antimicrobial coverage
  - bug-drug mismatch
  - no therapy
- Integrates VITEK® 1/VITEK® 2 ID/AST results with patient antibiotic therapy, bringing them to the clinician in real time
- Desktop and PDA application
- The Antibiotic Assistant
- The Dosing Assistant
- Therapy intervention documentation using the The Intervention Assistant™ from specific medications to generic activities

STELLARA Étage 3

- 25 pre-programmed automated alerts - increased alert functionality to include selected adverse drug events (ADEs)
- Integrates VITEK 1/VITEK 2 ID/AST results with patient antibiotic therapy, bringing them to the clinician in real time
- 4 automated antimicrobial alerts, as seen in Étage 2
- Desktop and PDA application
- The Antibiotic Assistant
- The Dosing Assistant
- Therapy intervention documentation using the The Intervention Assistant from specific medications to generic activities

STELLARA Étage 4

- 90 pre-programmed automated alerts
- Integrates VITEK 1/VITEK 2 ID/AST results with patient antibiotic therapy, bringing them to the clinician in real time
- Full laboratory results, such as chemistries, renal function test, liver function test and coagulation
- 4 automated antimicrobial alerts, as in Étages 2 and 3
- Desktop and PDA application
- The Antibiotic Assistant
- The Dosing Assistant
- Therapy intervention documentation using the The Intervention Assistant from specific medications to generic activities

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In the Technical Library you can view published articles, white papers, case studies, technical reports, educational brochures, package inserts, MSDS documents, procedures, symposium posters and abstracts, as well as Frequently Asked Questions about products.

Why Identify Resistance – Clinical Needs

The importance of determining resistance phenotypes for sucessful antibiotic therapy

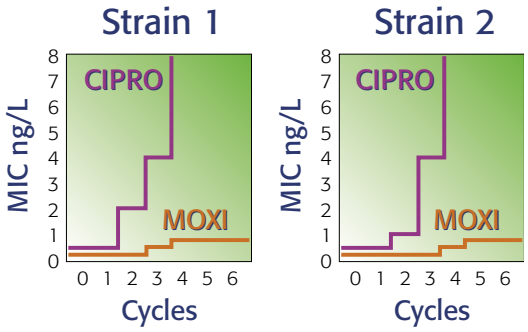
Medical microbiologists know that prescribing the best possible treatment is more complicated than recognizing a particular microbe's susceptibility or resistance to a given antibiotic. For each patient, it is important to understand the factors of resistance and know something about the person for whom the antibiotic is being prescribed. Resistance genes may, at times, mask unsuspected dangers, and the risk of treatment failure may be more substantial than what the culture dish tells us. There are a number of examples of the pitfalls of various bacterial species.

Pneumococci are responsible for acute otitis media, acute sinusitis, pneumonia, bacteremia and meningitis. These bacteria, which in the past responded to practically all antibiotics, have developed resistance to nearly all the drugs used to treat them, especially penicillins. With the notorious exception of meningitis, the therapeutic consequences of such resistance are limited. Indeed, pharmacokinetic data and clinical experience indicate that, except for meningitis, one can safely treat infections due to intermediate resistant pneumococci (MIC > 0.1 and < 2 mg/l) and even higher resistance levels (MIC > 2 mg/l) by increasing the doses of penicillins. In the case of meningitis, on the other hand, penicillin-resistant *Streptococcus pneumoniae* (PRSP) should never be treated with penicillin, regardless of the resistance phenotype. This is due to the fact that appropriate penicillin concentrations cannot be reached in the cerebrospinal fluid. The situation could become worse tomorrow if pneumococci develop high levels of resistance, as they appear to be doing in the United States. Be on the lookout for more news on this subject.

Staphylococci are problematic insofar as they may express resistance to methicillin or glycopeptide heterogeneously. How can one be sure that the most resistant bacteria have been tested for? What's more, highly resistant populations represent only a small proportion (102-105 CFU) of the much larger bacterial population present at the infected site (>109 CFU). The problem was recognized several years ago for methicillin-resistant staphylococci. Hence, appropriate methodological strategies were developed to recognize the phenotype. However, this is not yet the case with glycopeptide-resistant staphylococci, which have attracted attention only recently. Such organisms may still be missed by the diagnostic laboratory. Moreover, is it not possible that glycopeptide resistance has existed for a long time, but was masked by susceptible, rapidly growing bacterial populations?

Emerging resistance to fluoroquinolones is one of the most complex challenges facing physicians. Fluoroquinolones represent a very powerful and useful class of drugs in both human and veterinary medicine. Older molecules of this family were essentially targeted at Gram negative pathogens. Modern fluoroquinolones have an improved anti-Gram positive spectrum, and are thus recommended for the treatment of infections due to these types of bacteria as well.

However, if a patient is infected by a Gram positive bacterium that has previously acquired a resistance mutation to older quinolones, such as resistance to ciprofloxacin, this particular organism will have an increased chance of introducing a second mutation conferring high-level resistance to the newer quinolones. This hypothesis is not unrealistic since ciprofloxacin is one of the most commonly prescribed antibiotics in the world. Two treatment failures concerning levofloxacin were reported at the 2000 Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting (ICAAC): in both cases, the failure was due to a second gyrA mutation appearing in a bacterium already carrying a first resistance mutation in the parC genes. Both of them are typical quinolone-resistance mutations in Gram positive bacteria. Likewise, findings in Canada, where fluoroquinolones are widely prescribed for respiratory diseases, show that by combining such resistance mechanisms, pneumococci can develop resistance to the most recent molecules of this class. All together, this warrants caution against the overuse of these promising new drugs if one is to prevent the whole family of molecules from being lost at once.



The problem of extended-spectrum beta-lactamases (ESßL), which first arose in 1983, reached dramatic proportions in 1995. ESßLs are present in a number of enterobacteria. One of the most recent avatars, CTX-M, seems to have caused damage in Spain and has not spared France. ESßLs are also responsible for treatment failures and nosocomial epidemics of multi-resistant *K. pneumoniae*.

Detecting resistance is not an end in itself, but rather a means to establish the best possible treatment for a patient's bacterial infection. It also offers a still-frame picture of a never-ending story, the story of bacteria's resistance to antibiotics and of the genes responsible for resistance. Knowing the various phenotypes and genotypes is essential for both patient care and infection control.

Reprinted from bioMérieux's August 2001 issue of Identifying Resistance™ International Newsletter. Please watch for the next *bioMérieux Connection* for "Why Identify Resistance? Epidemiology Needs."

bioMérieux Connection

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