bioMérieux CONNECTION

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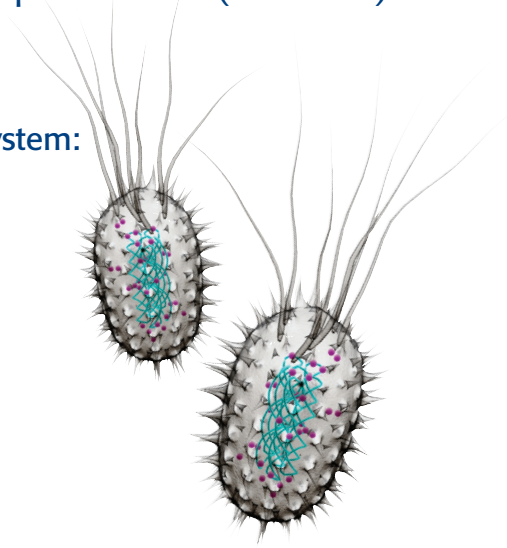


Message from bioMérieux

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

Welcome to the summer issue of the *bioMérieux Connection* newsletter. Already it has been an exciting year and I hope you enjoyed this year's ASM as much as I did. If you weren't able to make the trip, let me share some of the activities.

bioMérieux is constantly working to present educational programs that will be valuable to lab professionals every day. At ASM, we hosted a customer symposium on the impact lab personnel can have on preventing hospital-associated infections and emerging resistance. Industry leaders presented an educational series about new tools for laboratorians. This technology helps lab data support critical decisions made about patient care. As we do every year, we threw the best customer party of the ASM meeting and enjoyed spending time with friends and colleagues.

Finally, I am proud to announce a new campaign underscoring our approach to the work we do at bioMérieux – Empowering Clinical Decisions. We believe this is what we do for the healthcare industry and integrate it into every phase of development. At bioMérieux, we strive to provide instruments with accuracy and speed to make life a little easier for lab professionals. Ultimately, the work done in the lab is invaluable and provides the information necessary to Empower Clinical Decisions.

As always, I thank you for the continued support of bioMérieux products. We appreciate your business and wish you a safe and successful year.

from diagnosis,
the seeds of better health

BIOMÉRIEUX

bioMérieux Receives Major Order from BioMedical Laboratories

bioMérieux has received a major order from BML, Inc. (BioMedical Laboratories), the biggest Japanese private laboratory chain. bioMérieux will supply 28 VITEK® 2 XL to BML. The VITEK® 2 technology enables fully automated microbial identification and antibiotic susceptibility testing (ID/AST).

This technology offers faster results for relevant antibiotic therapy, thereby limiting the risk of therapeutic failure. For more than 40 years, bioMérieux has been committed to delivering relevant microbiology solutions to empower clinical decisions. bioMérieux's objective has always been to find new and better ways of improving overall patient care.

"We are very proud that BML has chosen our technology to equip its laboratories. This major order reinforces our leadership in microbiology," affirms Stéphane Bancel, CEO, bioMérieux.

Founded some 40 years ago, BML is an all-inclusive laboratory, offering a wide range of services such as special laboratory testing and investigative research. BML is committed to contribute to the progress of medical practice and to provide superior clinical testing systems for improved patient health. The company is also expanding in fields such as food hygiene testing, environmental analysis and genetic analysis. Information on BML can be found at www.bml.jp.

Scotland chooses VITEK® 2

National Procurement, a division of NHS National Services Scotland and the Scottish Microbiology Forum have awarded bioMérieux with a major contract to supply each of the 27 NHS clinical microbiology laboratories in the country with a VITEK 2 system for standardizing antibiotic susceptibility testing (AST) and bacterial identification.

The decision to standardize antibiotic susceptibility testing and bacterial identification is in line with the government's goal to provide better health for everyone in Scotland following the initiatives set out by the Scottish Executive in an important document entitled "Improving Health in Scotland – The Challenge." With reference to antibiotic prescribing, the objective is to provide timely and high quality surveillance data about existing and emerging bacterial resistance to antibiotics.

VITEK 2 was chosen after a thorough tender process of over 9 months, where a number of criteria e. g. price, after sales service & maintenance, health and safety and delivery were used to compare the merits of three automated systems available.

According to an official representative, the Scottish Microbiology Forum is extremely pleased to be associated with bioMérieux in this exciting project to provide standardized, automated AST to the whole of Scotland. This offers major benefits to patients, clinicians, microbiologists and epidemiologists in the ongoing battle with antibiotic resistance.

"This is a major success for bioMérieux. It demonstrates once again the strengths of VITEK 2 technology and our worldwide leadership in the field of automated microbiology," said Stéphane Bancel, CEO of bioMérieux.

VITEK 2 and its expert software Advanced Expert System, AES, offer significant benefits for the microbiologist, the clinician and, ultimately, the patient. In addition to optimized result reliability, the microbiologist can be confident that even weakly expressed resistance mechanisms will be detected. The microbiologist will obtain a rapid, accurate and validated test report, and can send it more rapidly to the clinician. This report helps the clinician to make the correct diagnosis and, when necessary, adapt the antibiotic therapy at the earliest possible stage. The patient benefits from timely treatment with the most relevant antibiotics.

VITEK 2 also contributes to the detection of nosocomial infections, enabling proactive measures to be implemented.

VIDAS® D-Dimer Exclusion™
Frequently Asked Questions

Calibrations:

1. How does one program a DD2 worklist?

- On a MiniVIDAS®:
  Status Screen – Select available section – enter "S1" in pos 1 and 2, enter "S2" in pos 3 and 4, followed by C1 and C2 in pos 5 and 6.
- On a VIDAS:
  Loading menu – Select assay DD2 – enter "S" in sample ID and calibration will load in predefined section as S1, S1, S2, S2, C1, C2.

2. What causes "invalid standards" on DD2?

- RFV too high, vortex samples thoroughly for 20 seconds.
- RFV too low, be sure to reconstitute with kit diluent.
- Reconstitution with syringes or serological pipettes (bulb/roller/mouth).
- CV% exceeded, be sure to pipette properly.

3. Where are S1, S2, and control (C1, C2) ranges located?
The ranges are located for each component on the MLE card for each kit lot.

4. Can calibrations be accepted if only part of it passes?
No, if any part of the calibration fails then the whole calibration must be repeated.

5. Can extra components of a DD2 be purchased separately?
No, all the components of a DD2 come as a kit.

6. What studies need to be done for DD2 on a regular basis?

- Calibrations need be done with every new kit lot and every 14 days afterwards.
- QCV tests need to be done monthly to check the pipetting system and optics.
- Linearity studies should be done every six months per CLSI guidelines.
- Proficiency testing should also be performed.

Linearity:

7. How is a DD2 linearity study done?
A linearity study is done with the components of a DD2 kit lot. Follow the following formula for 5 pool dilutions of 4 reps each:

- Pool 1 low sample (use the kit diluent)
- Pool 2 750 ul low + 250 ul high
- Pool 3 500 ul low + 500 ul high
- Pool 4 250 ul low + 750 ul high
- Pool 5 high sample (C1 from kit)

Stability/Storage:

8. Does DD2 have to come to room temperature and how long can the kit sit out?
No, the strips and spurs needed to run the assay are ready to use out of the refrigerator, no warm up is required. The rest of the kit should remain refrigerated. Reconstitution of S1, S2, C1, C2 requires 20 minutes or frozen aliquots will need to thaw, please refer to the DD2 package insert for further instructions.

9. How soon does a DD2 sample need to be separated after collection?
Samples should be centrifuged and tested within 4 hours after collection. Samples need to be centrifuged for 15 minutes and decanted into a plastic tube as soon as possible.

Stat Spins:

10. Are Stat Spins validated for DD2 assays?
No, customers must perform their own validation studies for Stat Spins.

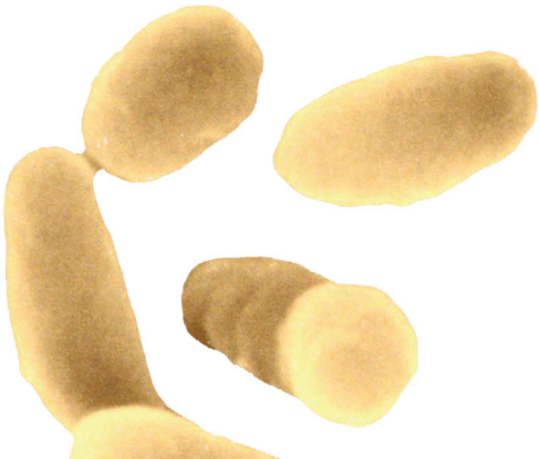
VIDAS® D-Dimer EXCLUSION™

macrolides and related

Roland Leclercq, MD, PhD, is professor of microbiology. He is currently head of the Microbiology department of the University-Hospital of Caen, France. He also serves on the French Committee on Antimicrobial Susceptibility Testing. His longstanding interest on mechanisms of antimicrobial resistance in Gram positive organisms, in particular resistance to glycopeptides and macrolides, led to the publication of about 150 papers in peer reviewed scientific journals.

The macrolides have been known for more than five decades and since the introduction in therapy of erythromycin, a number of these molecules have been developed for clinical use. Macrolides have a common structure formed by a large lactone ring. Erythromycin is a mixture of antibiotics that includes erythromycin A which is the active compound and has a fourteen-membered lactone ring with two sugars, L-cladinose and an amino sugar. Other commercially available macrolides derived from erythromycin A and include clarithromycin, dirithromycin, roxithromycin, and azithromycin, which has an enlarged 15-membered ring resulting from a nitrogen insertion. The structural modifications of erythromycin A resulted in improved pharmacokinetic profiles and better tolerance but could not overcome cross-resistance between members of this class of antimicrobials. The recently developed ketolide, telithromycin, is derived from clarithromycin and has two major modifications, replacement of L-cladinose by a keto-function and a 11-12-carbamate extension with an arylalkyl modification, which may explain increased intrinsic activity and activity against erythromycin-resistant strains. Other antimicrobials although structurally different are related to macrolides because they share a

structural modifications of erythromycin A resulted in improved pharmacokinetic profiles … but could not overcome cross-resistance between members of this class of antimicrobials



similar mode of action and crossresistance to a certain extent. Together with the macrolides, they form the MLS (macrolides-lincosamides-streptogramins) group of antibiotics. Lincosamide antibiotics (clindamycin and lincomycin) are devoid of a lactone ring. The streptogramins (quinupristindalfopristin, pristinamycin available in a few countries and virginiamycin for veterinary use) represent a strategy to overcome macrolide resistance. These antimicrobials are composed of two streptogramin factors, A and B, with a synergistic activity resulting from dual interaction with the ribosome.

Table 1 Major phenotypes and genotypes of macrolides resistance in Gram-positive cocci due to ribosomal methylation, drug efflux, or drug inactivation.

SPECIES	MECHANISM	GENE CLASS	PHENOTYPE DESIGNATION	PHENOTYPE OF RESISTANCE			
				14-, 15-Md	Tel	16-Md	Cli
Staphylococcus sp.	Ribosomal Methylation	erm(A), erm(C)	MLSB inducible	R	s	s	S
			MLSB constitutive	R	R	R	R
	Macrolide Efflux	msr(A)	MSB	R	S	S	S
Streptococcus and Enterococcus sp.	Ribosomal Methylation	erm(B)	MLSB inducible	R or I	S	R or I or S	R or I or S
		erm(TR)	MLSB constitutive	R	R	R	R
	Efflux	mef(A)	M	R	S	S	S

14/15/16-Md: 14/15/16-membered ring macrolides: read overleaf the list of antibiotics Tel: telithromycin, Cli: clindamycin
R, resistant; S, susceptible; I, intermediate resistance; s, susceptible *in vitro* but risk of selection of constitutive mutants *in vivo*

antibiotics

Due to this property, these molecules may retain activity against Gram-positive organisms displaying resistance to a single factor.

Bacteria Have Several Ways to Resist Macrolides

The spectrum of activity of macrolides is limited by the intrinsic resistance displayed by most Gram-negative bacilli to these compounds. However, certain clinically important Gram-negative bacilli, such as *Bordetella pertussis, Campylobacter, Chlamydia, Helicobacter,* and *Legionella* are important exceptions.

Further, the Gram-positive microorganisms have collected mobile elements that help them evade the lethal effects of antibiotics. Bacteria have developed three ways of resistance against MLS antibiotics: 1) target site modification that prevents the binding of the antibiotic to its natural target, the ribosome, 2) efflux of the antibiotic which prevents the antimicrobial from reaching the ribosome and 3) inactivation of the antimicrobial molecule.

Resistance to Macrolides By Efflux

Acquired resistance to macrolides by active efflux has been detected in various bacterial species including streptococci and staphylococci.

The efflux proteins conferring acquired macrolide resistance usually found in *Staphylococccus* spp. are ABC-transporters encoded by plasmid-borne *msr* genes. The resistance is inducibly expressed. Erythromycin and other 14- and the 15-membered macrolides are inducers whereas streptogramins B are not. Therefore the strains are resistant to streptogramins B only after induction with erythromycin. Clindamycin is neither an inducer nor a substrate for the pump and thus the strains [+]

(continued on page 6)

The macrolide antibiotic class has been used as **first-line therapy** to treat various bacterial infections including respiratory infections **since the development of erythromycin in the 1950's.**

Due to its frequent use and the development of other drugs in the macrolide class, **macrolide resistance has increased rapidly throughout Europe and North America in recent years.**

Resistance, that is now common in staphylococci and streptococci, is attributable to two mechanisms both of which are readily transmissible. As a result of the increased resistance in commonly treated respiratory pathogens, **susceptibility testing is recommended in the case of treatment of serious illness** such as community acquired pneumonia, particularly if the patient is allergic to ß-lactams and quinolones.

(continued from page 5)

[-] are fully susceptible to this antimicrobial *(Table 1)*. This phenotype can be easily distinguished from the MLSB inducible phenotype by the lack of interaction between erythromycin and clindamycin.

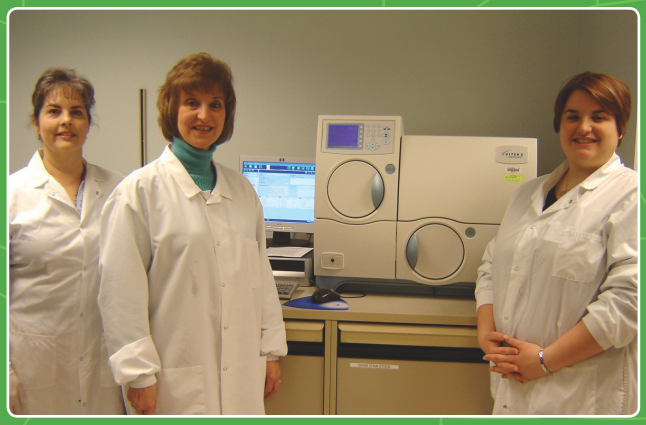
The *msr*(A) gene has not been found in streptococci. In streptococci, the genes responsible for efflux belong to the *mef*(A) gene class and are part of closely related large transposable elements. Resistance is expressed at moderate levels with erythromycin MICs comprised between 1 and 64 µg/ml (generally between 8 and 32 µg/ml). Because the 16-membered macrolides, the lincosamides, and the streptogramins B are not substrates of the pump, these antimicrobials remain active, even after induction with erythromycin. Resistance to erythromycin combined with susceptibility to clindamycin, whether the cells are induced or not with erythromycin, defines the M phenotype. Again, this phenotype can be easily distinguished from the MLSB inducible phenotype by the lack of interaction between erythromycin and clindamycin. ▮

It is an honor to have a column on this subject written by Prof. Roland Leclerq. Prof. Leclerq is one of the world's experts on the variety of ways that pathogens have invented to become resistant to this widely used antibiotic class.

— Dee Shortridge, PhD
Director R&D Microbiology
in Saint-Louis

[↖] *To read the complete article on Macrolides, go to www.biomerieux-usa.com/connection*

FINAL STOP: TIFFIN, OH



Microbiology Team Mercy Hospital Tiffin Left to right: Jean Smith, Janet Lane (Supervisor), and Diana Brown

The VITEK® 2 Compact in action. Part 3 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. In previous issues, we visited with Joe Laynor at Winn Army Hospital in Fort Stewart, Georgia, and Zack Blair, who works at Perry County Hospital in Tell City, Indiana.

This month, our travels conclude in Tiffin, Ohio, where we meet up with Janet Lane, Microbiology Supervisor at Mercy Hospital.

Junior grows up.

Mercy is a 100-bed acute care facility that's part of seven-hospital regional healthcare system. We've had our VITEK 2 Compact for about a year and a half now.

The changeover was initiated when the hospital decided to upgrade its LIS, but really the decision goes back to 1999 – that's when we made the switch to the VITEK Junior system. We had been using a competitor's platform, but when we looked at all the systems back then we liked the reliability of the results and the expert system with the Junior.

We've been pleased with both the equipment and with bioMérieux as a company. So in 2005 when we were looking for a new system, we looked around at everything again, and chose the VITEK 2.

It had some great updates, a very expanded organism database, it required very little maintenance – and minimal daily preparation of the cards.

We wouldn't have to write on them anymore, which was wonderful.

As in all industries, healthcare is dealing with productivity issues; we need to be as efficient and productive as possible with limited staff – and still try to get information to the physicians quickly, so a patient's stay can be shorter, and outcomes can be better.

A perfect fit.

Overall, the VITEK 2® fit into our climate the best, and gave us quality answers with minimal intervention and offline testing. Most of the time we can load it by nine in the morning, and we're able to turn these out by early afternoon; by 4:00 most of our work is out the door.

Many of the IDs, especially the gram negatives, come off the system faster, and the antibiotic susceptibility testing comes off faster. Most of the gram negatives and many gram positives can be turned out the same day.

The expanded database and the Advanced Expert System (AES) have made a big difference. In the past we might have sent a number of isolates to the reference lab. The ones that we just hadn't identified on the previous equipment, we're now getting answers – we go to the books and, "wow, this is it!" So consequently our turnaround time is much better.

And of course our physicians were accustomed to rapid turnaround time because of the way we had developed our workday. So we still had to meet or exceed their expectations, and for that the VITEK 2 was the best system.

I know our pharmacists look at these results, make their adjustments – make sure first of all that it's an effective antibiotic they're giving. They look at being able to switch from IV to oral drugs rapidly, so that they can send patients home as quickly as possible. They're using our results to intervene and make recommendations to the physicians.

A better connection.

OBSERVA® is our connection to the LIS, but it's also more than that. We're downloading patient demographics, I'm using it to do my blood culture contamination rate reports. Sometimes, I find it better than the LIS for pulling things like how many MRSAs I have, how many VREs I've had. It's a good management and administrative tool for epidemiology. There are some built-in reports and searches, and I can set up my own parameters and get the information I want.

We've liked being able to use OBSERVA's CAR rules, and being able to send the interpretations from there to the LIS. We use VITEK's rules and the CAR rules that bioMérieux has written, plus a few of our own. And we're able to update them with CLSI changes, which is very helpful.

"I have to say, we've been more than satisfied. I think it's gone beyond what we've expected."

Previously we felt that some of these drugs maybe shouldn't be reported but we were always hesitant to change it to "resistant." Now, the AES says "yes you should" – so it gives us the confidence to do what we really felt we should be doing all along. Being a small hospital, we don't have a PhD microbiologist or an infectious disease doctor. The AES is great in helping us interpret and understand the mechanisms of resistance, so we can better explain it if the physician asks.

We're very fortunate to have Bryan Williamson as our Client Consultant. He had been in-house in development and training, and that gives him a unique perspective. He certainly has an expanded understanding of people's issues and problems. Sometimes there's a quick little question we want to ask, and he's very quick to respond. I have the confidence in him to let me know of things that are rapidly changing, or something they've found that we need to be aware of – so we don't have to learn the hard way.

As far as using the system, we have people with different skill levels, and the trainers work well with that. Our technical service rep gave the lunch-and-learn on the AES, and we had a peer audio conference on some of the new mechanisms of resistance. That certainly alerts us to be looking for these things and helps us understand when we do see them.

DiversiLab System: Strain Typing

The DiversiLab, System for DNA fingerprinting and analysis is a powerful tool for tracking the spread and source of microbial infection, contamination, or epidemics natural and man-made. Based on patented rep-PCR technology, microbial isolates can quickly and accurately be distinguished at the subspecies and strain level.

DiversiLab can provide automated strain typing in about 4 hours. The System also facilitates epidemiological studies with standardized protocols and reagents, assays for bacteria and fungi and provides local and reference data storage. For more information please visit www.biomerieux-usa.com/barcodes. ▮

Education Center – Now Live!

As you know, bioMérieux has a strong emphasis for 2007 on training and educating our customers. To better assist our customers in gathering training and educational opportunities we have created a new online Education Center. This site has resources to empower you with the tools to make the best decisions for your institution. Resources include PACE Approved Programs, Webinars, Training Demos, Upcoming tradeshows and much more. Visit www.biomerieux-usa.com/education for more details. ▮

2007

SHOWS AND CONFERENCES

Association of Public Health Laboratories
Jacksonville, FL • June 3-5 – *Booth #29*

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.