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Putting it Into (Best) Practice: Diagnostic Challenges and Opportunities in Pneumonia CME

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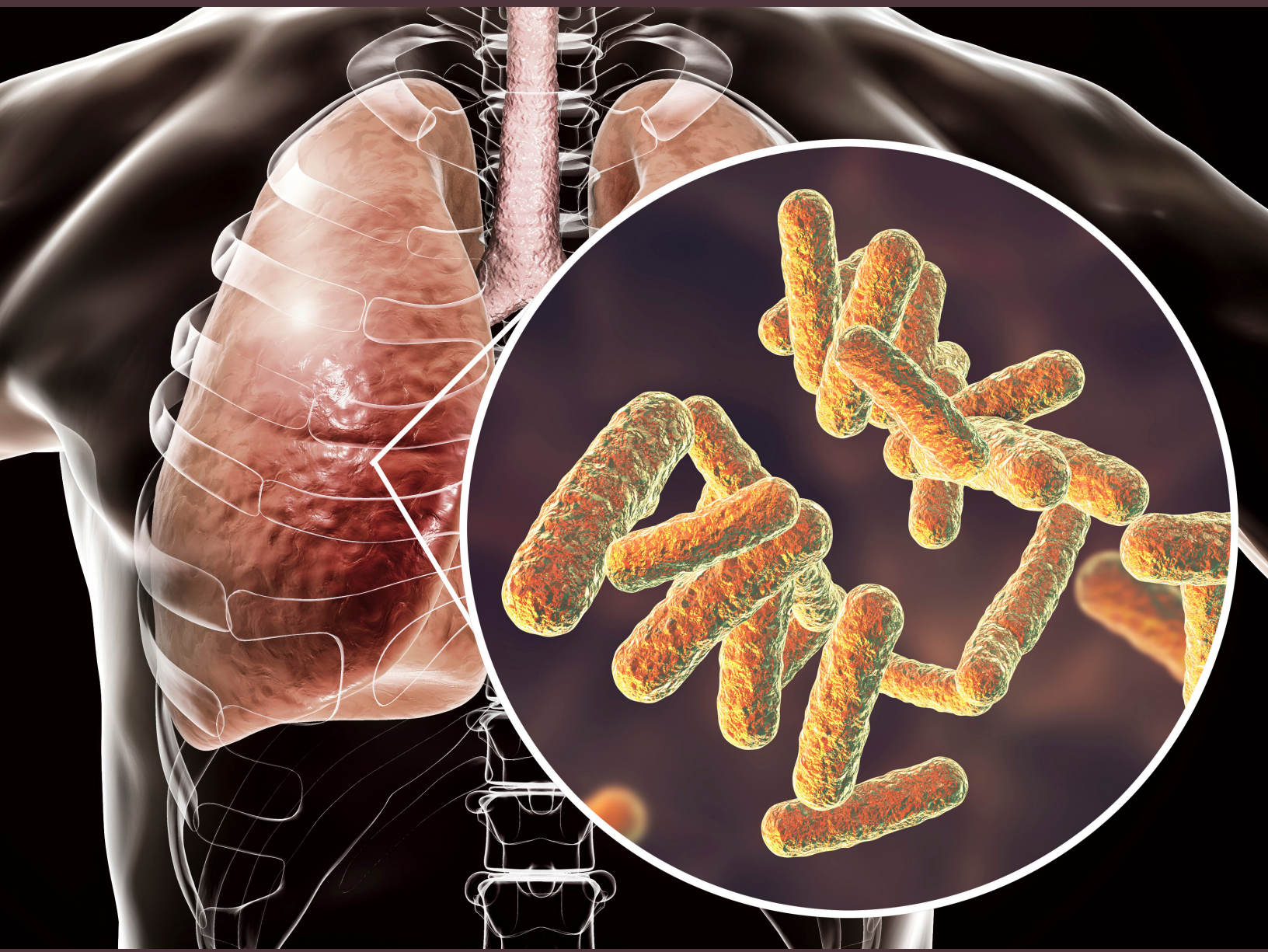

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Target Audience
This activity is intended for emergency medicine, infectious disease, and pulmonary medicine specialists.

Goal Statement
The goals of this activity are to inform clinicians regarding the use of rapid diagnostic tests to diagnose pneumonia and respiratory tract infections and to increase awareness regarding antibiotic stewardship.

Learning Objectives
Upon completion of this activity, participants will:

Have increased knowledge regarding the
- Latest data on the use of pneumonia multiplex panel tests
- Key characteristics of rapid diagnostic tests for pneumonia

Have greater competence related to
- Incorporating multiplex panel tests for pneumonia into patient care

Credits Available

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Received grants for clinical research from: Allergan; Contrafect; Nabriva

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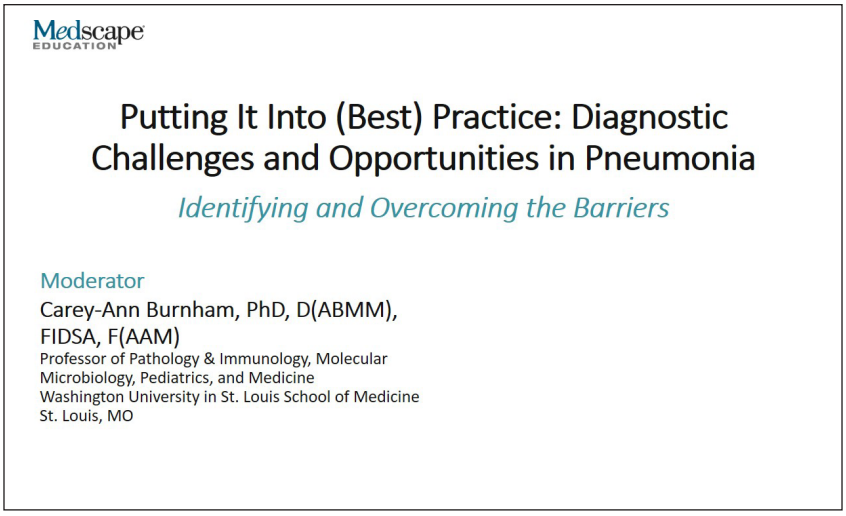
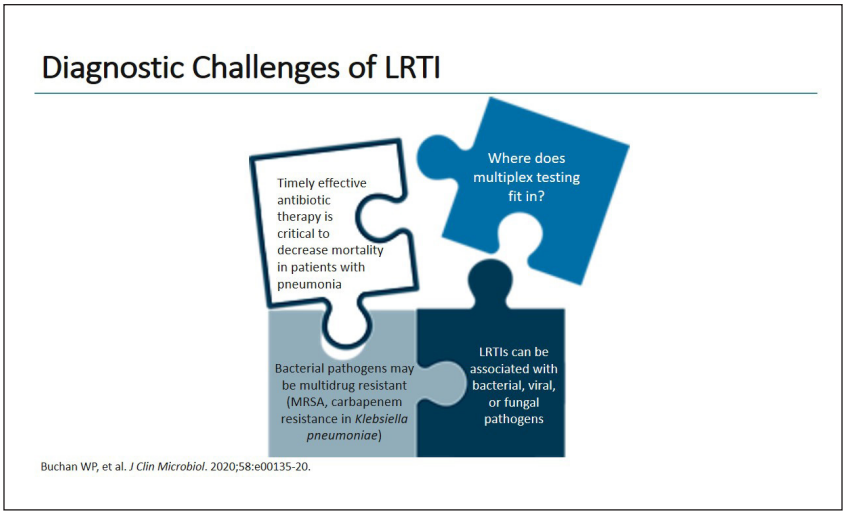


Putting It Into (Best) Practice: Diagnostic Challenges and Opportunities in Pneumonia: Identifying and Overcoming the Barriers

Carey-Ann Burnham, MD: Hello and welcome. I'm Carey-Ann Burnham, a Professor of Pathology and Immunology, Molecular Microbiology, Pediatrics and Medicine at Washington University in St. Louis. I'm also the Medical Director of Clinical Microbiology at Barnes Jewish Hospital. I would like to welcome you to this program titled: Putting It Into Best Practice, Diagnostic Challenges and Opportunities in Pneumonia.

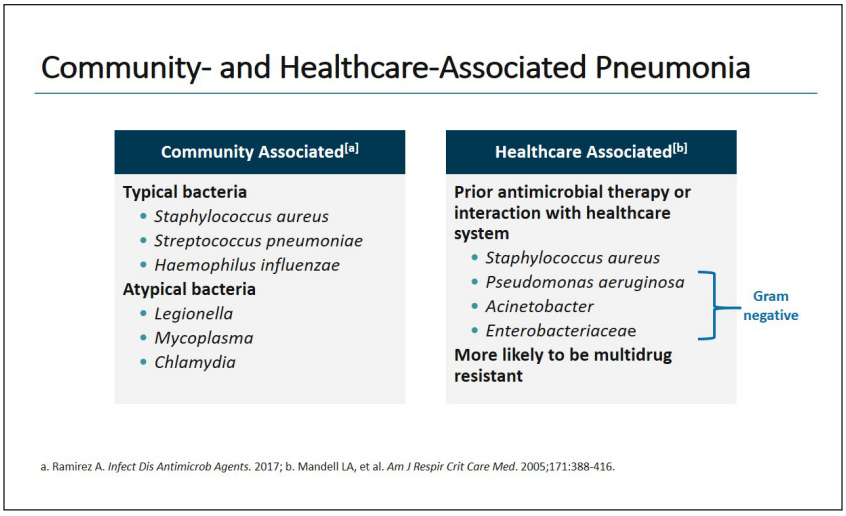
Panelists

I'm really excited that joining me today are Amy Leber, who's a Clinical Professor of Pediatrics and Pathology, at the Ohio State University College of Medicine, and Director of the Clinical Laboratories, as well as Clinical Microbiology and Immunoserology at Nationwide Children's Hospital in Columbus, Ohio. And Gregory Moran, who's the Chief of the Department of Emergency Medicine, and faculty in the division of infectious diseases at Olive View UCLA Medical Center, and Professor of Clinical Emergency Medicine at the David Geffen School of Medicine at UCLA in Los Angeles, California.



Diagnostic Challenges of Lower Respiratory Tract Infections (LRTI)

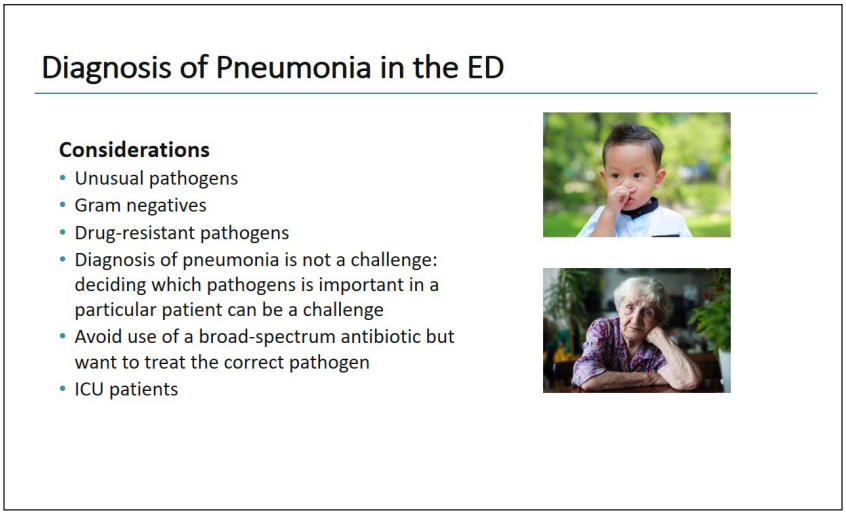
Today, we're here to talk about lower respiratory tract infections, which are an important cause of morbidity and mortality. These infections can be challenging to diagnose because they can be associated with bacterial, viral or fungal pathogens. And making this worse, the bacterial pathogens may be multidrug resistant, such as methicillin resistance in staph aureus, or carbapenem resistance in Klebsiella pneumonia. It has been well demonstrated that timely effective antibiotic therapy is critical to decrease mortality in patients with pneumonia. Today we're here to focus on the use and implementation of some of the newer multiplex panels for the diagnosis of pneumonia.



Community- and Healthcare- Associated Pneumonia

Broadly, pneumonia can be sub-classified into community associated and healthcare associated. In community associated, some of the heavy hitters include so-called typical bacteria, such as staphylococcus aureus, streptococcus pneumonia, and Hemophilus influenza. The so-called atypical bacteria, such as Legionella, mycoplasma, and chlamydia and respiratory viruses such as influenza and respiratory syncytial virus.

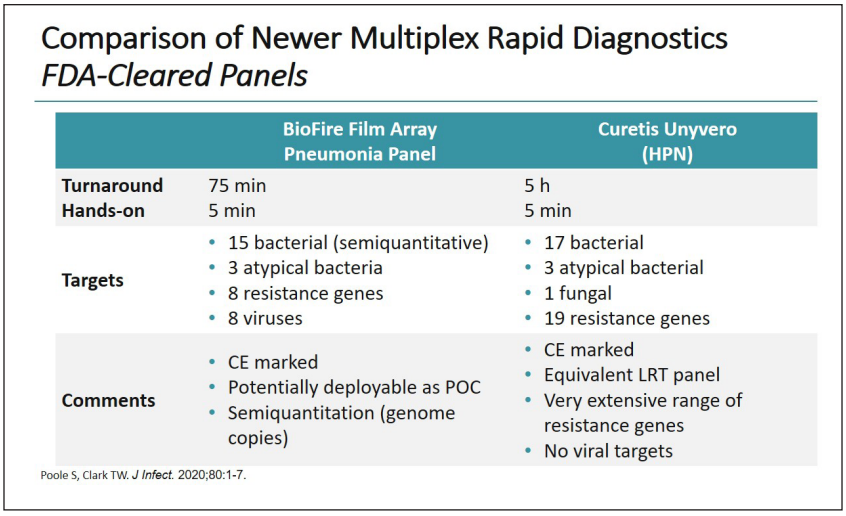
Although the phrase healthcare-associated pneumonia has generally fallen out of vogue, it's a nice way of encapsulating those patients with different risk factors, such as those that have seen a lot of antimicrobial therapy or have had a lot of experience with the healthcare system. Staphylococcus aureus is an important pathogen in this group, but we're more likely to see gram negatives such as pseudomonas aeruginosa, Acinetobacter, and the Enterobacteriaceae. As well, patients that have had a lot of healthcare exposure are more likely to be infected with multidrug resistant organisms. Greg, what is your experience with some of these patients?



Diagnosis of Pneumonia in the Emergency Department

Gregory Moran, MD: In my practice, I work in the emergency department, I'm at a busy county hospital in Los Angeles. We see a broad mix. We see everything that rolls in the door, everything from little kids to old people from nursing homes. It is a challenge to try to know how big we want to go for our empiric treatment. In emergency departments, we want to move fast. We want to be able to do a quick assessment, do a correct assessment and make the right diagnosis.

Challenge in the emergency department, it's usually is not so much making the diagnosis of pneumonia, which is pretty straightforward, but it's trying to decide, "Okay, do I need to worry about unusual bugs? Do I need to worry about gram negatives? Do I need to worry about super resistant bugs?" so that's going to be the challenge. We don't end up just doing sort of the big shotgun approach for everybody and trying to cover every possible pathogen. But at the same time, we want to make sure that we do get the pathogen that's there. In particular, in people who are really sick, people who have signs of severe sepsis, like the ICU-level care type patients.



Comparison of Newer Multiplex Rapid Diagnostics
FDA-Cleared Panels

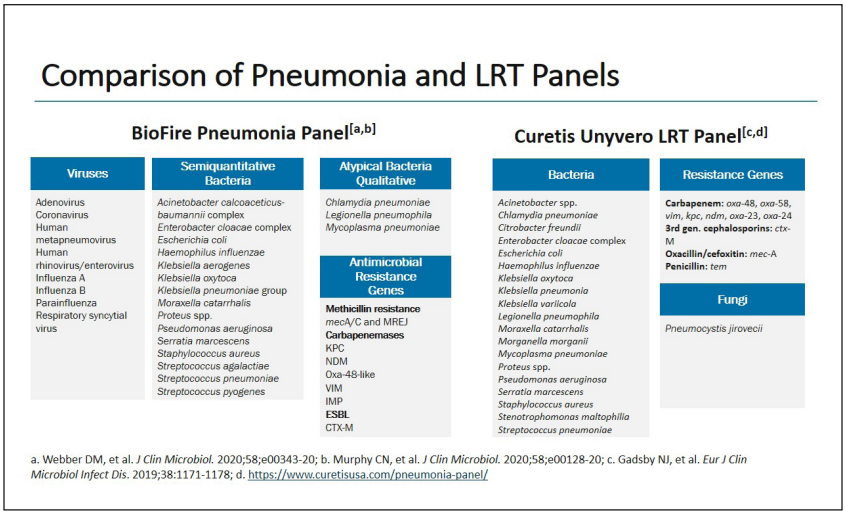
	BioFire Film Array Pneumonia Panel	Curetis Unyvero (HPN)
Turnaround **Hands-on**	75 min 5 min	5 h 5 min
Targets	• 15 bacterial (semiquantitative) • 3 atypical bacteria • 8 resistance genes • 8 viruses	• 17 bacterial • 3 atypical bacterial • 1 fungal • 19 resistance genes
Comments	• CE marked • Potentially deployable as POC • Semiquantitation (genome copies)	• CE marked • Equivalent LRT panel • Very extensive range of resistance genes • No viral targets

Poole S, Clark TW. *J Infect.* 2020;80:1-7.

Comparison of Newer Multiplex Rapid Diagnostics: FDA-Cleared Panels

Dr Burnham: With that, Amy, would you mind telling us a little bit about the differentiating characteristics of these newer multiplex panels?

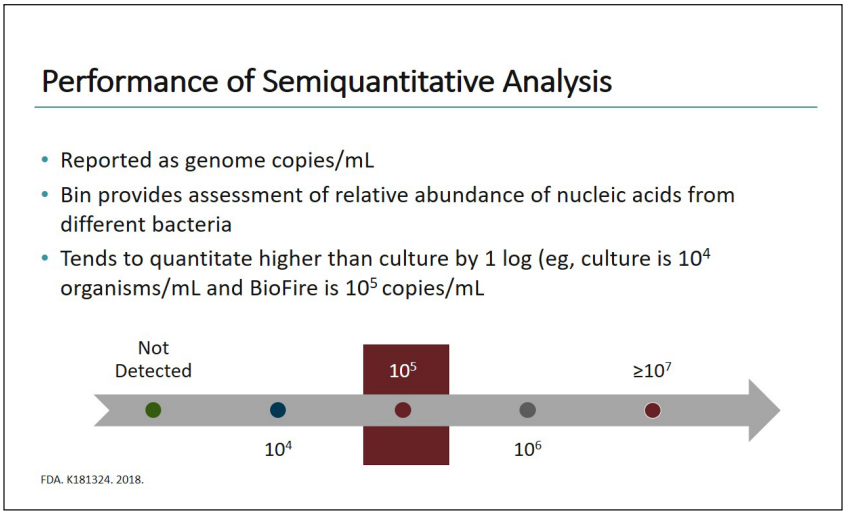
Amy Leber, PhD: I'm working at a pediatric institution, where I deal with microbiology, basically, and molecular micro. While we do have children, we see people all the way up to adults. So, it is important for us to be able to diagnose pneumonia. Currently, there are two FDA-cleared panels in the United States, and we will touch on both of those. But as we look at their characteristics, one is turnaround time. If we're to really have an immediate effect, we want it to be rapid. We see, the FilmArray takes about 75 minutes with 5 minutes hands on time, as opposed to the Unyvero, which takes about five hours with five minutes hands on time. If we look then at the actual components of each of these panels, you'll see they have, what Carey-Ann said, were the kind of normal or typical bacteria, also atypical bacteria. Then for the Unyvero tester includes pneumocystis, that's unique.



a. Webber DM, et al. *J Clin Microbiol.* 2020;58;e00343-20; b. Murphy CN, et al. *J Clin Microbiol.* 2020;58;e00128-20; c. Gadsby NJ, et al. *Eur J Clin Microbiol Infect Dis.* 2019;38:1171-1178; d. https://www.curetisusa.com/pneumonia-panel/

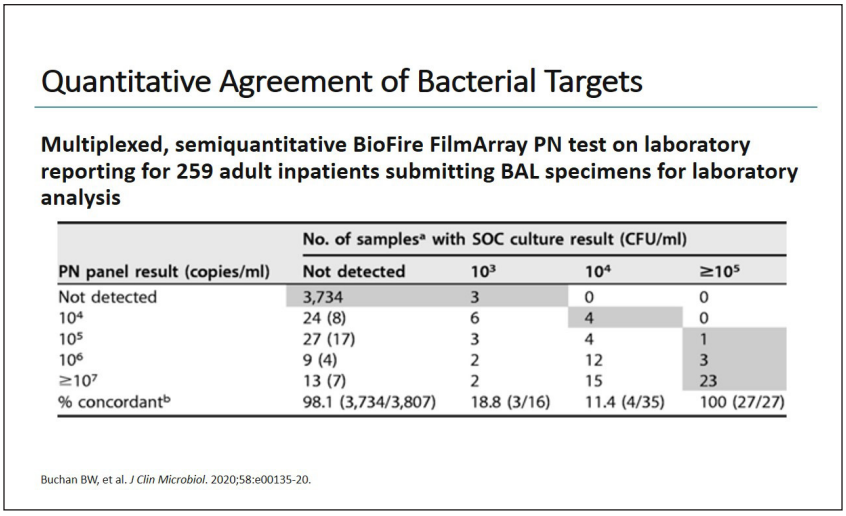
Comparison of Pneumonia and LRT Panels

Both panels have resistance genes. Here, you see the Unyvero test has detection of carbapenems, ESBLs, MRSA and then penicillin. A broad range of targets, including antimicrobial resistance. In contrast, the FilmArray pneumonia panel has the bacteria, the atypical bacteria, the differences are, it includes viruses and we don't usually screen all our lower respiratory tract samples for viruses. Another key difference is it has a semi-quantitative analysis for the typical bacteria. We'll discuss this in a little bit and how important that is. It will help Greg and others related to culture.



Performance of Semi-quantitative Analysis

If we go and think about one of the aspects, is the semi-quantitation. What happens is there's a control put to the mix that has a known quantity. When the test is performed, there's a semi quantitative analysis compared to that control, it allows it to be put in what's called bins in terms of genome copies per mil. It is going to report out, similar to a culture, in that it has 10 to the 4th, up to 10 to the 7th. And that relates a little bit to culture, but not totally, in that the molecular methods are more sensitive, so they tend to over quantify. In essence, this allows you to get a relative assessment of quantity because`, Greg can tell us, but usually pneumonia is a single organism agent. When we get multiple targets, it's nice to be able to say, "What is the one there in the highest quantity?"



Quantitative Agreement of Bacterial Targets

Multiplexed, semiquantitative BioFire FilmArray PN test on laboratory reporting for 259 adult inpatients submitting BAL specimens for laboratory analysis

	No. of samples[a] with SOC culture result (CFU/ml)			
PN panel result (copies/ml)	Not detected	10^3	10^4	$\geq 10^5$
Not detected	3,734	3	0	0
10^4	24 (8)	6	4	0
10^5	27 (17)	3	4	1
10^6	9 (4)	2	12	3
$\geq 10^7$	13 (7)	2	15	23
% concordant[b]	98.1 (3,734/3,807)	18.8 (3/16)	11.4 (4/35)	100 (27/27)

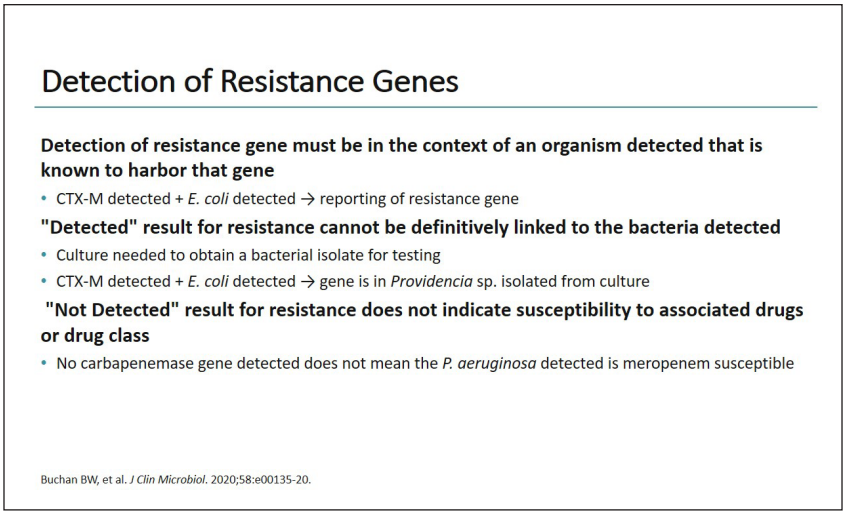
Buchan BW, et al. *J Clin Microbiol*. 2020;58:e00135-20.

Quantitative Agreement of Bacterial Targets

Then the other, if we look at a study here, this is just showing where we look at culture in a study of BALs compared to the molecular test. Here we see some, where the culture is negative, will be detected on the panel. The correlation is not one to one in terms of quantity, again, the idea is it over quantifies, and it will detect things that culture can miss.

Dr Burnham: Your lab was part of that study. That's a great study.

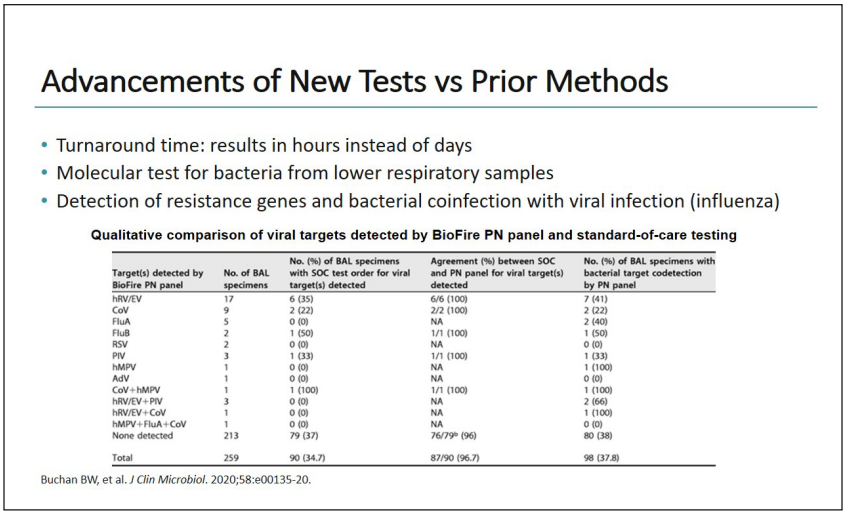
Dr Leber: We participated in the clinical trial that tested around 1600 samples. This paper is a sub-analysis of some data to look at potential clinical outcomes, because as we'll discuss, there really aren't any true prospective studies which we need.



Detection of Resistance Genes

I think what Greg really wants to understand, the clinician needs to know about resistance genes. This is another one of the big advances to be able to rapidly tell. How this works is, there are the panel of resistance genes, but they have to be paired when positive with a bacteria that contains that gene. For example, if you detect CTX-M or an ESBLG and E. coli is there, it will be reported. However, just because you have E. coli and CTX-M doesn't mean that gene is in the E. coli. For example, if you culture it, you may have a providencia bacteria, not on any of the targets that actually contains that gene. That's important for clinicians to understand.

Then most importantly is, I think clinicians tend to think of molecular as an absolute, and they really learn to trust the results. But and not detected for resistance gene doesn't necessarily rule it out. For example, if you have pseudomonas and there are no carbapenemase genes detected, you could still have a carbapenem resistant pseudomonas due to another mechanism like a Porin resistance. There's a lot to learn, to relate back to culture in particular, to help us understand these newer methods.



Advancements of New Tests vs Prior Methods

- Turnaround time: results in hours instead of days
- Molecular test for bacteria from lower respiratory samples
- Detection of resistance genes and bacterial coinfection with viral infection (influenza)

Qualitative comparison of viral targets detected by BioFire PN panel and standard-of-care testing

Target(s) detected by BioFire PN panel	No. of BAL specimens	No. (%) of BAL specimens with SOC test order for viral target(s) detected	Agreement (%) between SOC and PN panel for viral target(s) detected	No. (%) of BAL specimens with bacterial target codetection by PN panel
hRV/EV	17	6 (35)	6/6 (100)	7 (41)
CoV	9	2 (22)	2/2 (100)	2 (22)
FluA	5	0 (0)	NA	2 (40)
FluB	2	1 (50)	1/1 (100)	1 (50)
RSV	2	0 (0)	NA	0 (0)
PIV	3	1 (33)	1/1 (100)	1 (33)
hMPV	1	0 (0)	NA	1 (100)
AdV	1	0 (0)	NA	0 (0)
CoV+hMPV	1	1 (100)	1/1 (100)	1 (100)
hRV/EV+PIV	3	0 (0)	NA	2 (66)
hRV/EV+CoV	1	0 (0)	NA	1 (100)
hMPV+FluA+CoV	1	0 (0)	NA	0 (0)
None detected	213	79 (37)	76/79[b] (96)	80 (38)
Total	259	90 (34.7)	87/90 (96.7)	98 (37.8)

Buchan BW, et al. *J Clin Microbiol*. 2020;58:e00135-20.

Advancements of New Tests vs. Prior Methods

Dr Burnham: That's a great point. Thanks, Amy so much for giving us that great description of how the tests work as we started to think about implementing them in our laboratories. What do you think are some of the things that are really the big advantages or the major advancements in these compared to our prior methods?

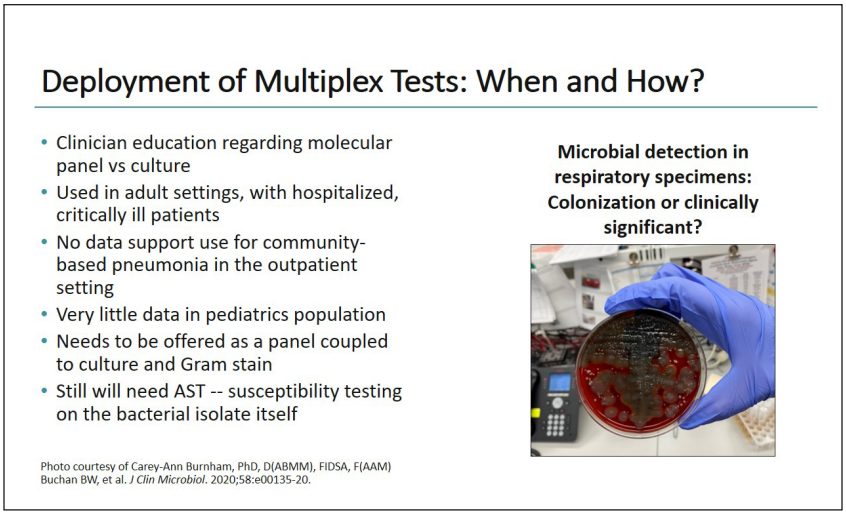
Dr Leber: Turnaround time is obviously one. If you could get a result in hours instead of days, that helps the clinician, particularly in the practice of emergency medicine, I would imagine Greg, that's critically important to be able to move patients through.

Dr Moran: Yes.

Dr Leber: We've never had a test to detect bacteria routinely and lower respiratory samples with a molecular test. Also this detection of resistance genes will be critical. And then I'd kind of like to bounce something off of Greg. If we look at this slide, this table, this again is from the FilmArray pneumonia panel, looking at a subset of 259 BALs, but it's just showing you the concept that we don't know normally screen routinely and thoroughly for viruses. In this table, we're looking at the number of BALs with the detections by the molecular method, and then showing you how many had that actual test ordered for standard of care. And it's much, much lower. I'm curious, Greg, if you think that routine and comprehensive screening for viruses in these patients will have an impact?

Dr Moran: The answer is yes. I think it will. There's actually a couple of interesting things to look at here. First of all, there are some viruses that we are pretty commonly testing for, especially during flu season. We very routinely, when people are coming in with respiratory symptoms. My own hospital, we have a rapid test that we can get back pretty quickly. That's a combination, flu and RSV, that's a very common thing. A lot of places have a rapid influenza test that they can get. And that's reassuring. It's nice to know that they have influenza. If they're sick enough to be in the hospital and may need prompt antiviral treatment that we're going to give them. But one of the big questions that always remains is, is there a super infection on top of that, a bacterial superinfection? Because we know that's often-what kills people with influenza and sometimes with other respiratory viruses.

I know what happens in practice is very often these patients end up getting antibacterials, even with a positive flu test. As we see in this slide, it was not uncommon that they found co-infection. It is nice to know with the test that not only is there a virus present, but whether there is, or is not a bacterial co-infection going on at the same time, because will absolutely impact our treatment for these patients. If we only test for bacteria and we don't find it, then we may not be so confident that we can forgo antibiotics. If we have a test that tells us, one, there's no bacterial pathogens identified, and two, we actually did find a viral pathogen that would explain these symptoms, we would be far more comfortable with holding the antibacterials in that case and just focusing on the antiviral treatment.



Deployment of Multiplex Tests: When and How?

Dr Burnham: Thanks, Greg. Amy as laboratorians, there's a lot of different technologies coming to the lab. We have to think about when and how to deploy. How are these multiplex tests for pneumonia being deployed in the current clinical context?

Dr Leber: It's interesting, these are not yet rapidly in use across the United States. And part of that has to do with some learning that needs to take place in terms of how it compares to culture. But certainly I think it has been deployed in adult settings, in patients that are very sick needing hospitalization. I don't think we have data to support its use in the community, that is community-based pneumonia that's treated in the outpatient setting. And pediatrics, there's very little data. I think one of the things in deploying it, you're going to have to decide, do you limit its use? And I know Greg is actually using it at Olive View and there is some, he can comment on this, some restriction in its use.

Then from a laboratory point of view, we really need to think about how it's offered. This cannot be offered without being coupled to, as a panel, culture and gram stain. That's because these don't cover all bacteria, for example, present in sputum or lower respiratory tract samples. Additionally, we use gram stain in the lab in a very important way. We use it to assess the quality of the sample. If it's spit, we can tell, and we won't bother culturing it. The question is, do you use those sign criteria for the use of a molecular test? We've debated this, Carey-Ann and I, about how that might happen. And you may choose to limit it used to only those quality samples. There is a lot to learn in that regard. And certainly we're still going to need AST testing, susceptibility testing on the bacterial isolated itself is still very necessary. We covered some of that earlier on.

In terms of, I think really the critical need is to educate clinicians about its use compared to culture. If we look in this slide, we see a culture plate. This shows you a sputum plated on blood agar. You can see there's a lot of different types of bacteria, and there's definitely a predominant bacteria that's pseudomonas. Two things here, we can have things in culture that overgrow others, so we can miss more fastidious bacteria. The other thing is we can have specific practices based on each laboratory about how they report normal flora. For example, staph aureus in very low numbers may be grouped as normal flora, but yet in a molecular panel, it will be called out. So really, I think as we implement this, we really need to educate our clinician friends to help them use the test to its fullest.

Dr Burnham: Absolutely. And that picture of that culture plate is just an all too familiar scene.

Dr Leber: Yes

Most Common Organisms Detected in Lower Respiratory Tract Samples

		Bacterial Targets				Viral Targets		
Study	Test	1	2	3	4	1	2	3
Murphy[a]	BioFire	*S. aureus*	*H. flu*	*PSA*	*M. Cat*	*RV/EV*	*RSV*	*Corona*
	Culture	*S. aureus*	*PSA*	*H. flu*	*Kleb pneumo*	—	—	—
Webber[b]	BioFire	*S. aureus*	*H. flu*	*PSA*	*E. cloac* complex	*RV/EV*	*Flu A*	*Corona*
	Culture	*S. aureus*	*H. flu*	*PSA*	*E. coli / E. cloac* complex	—	—	—
Collins[c]	Univero	*S. aureus*	*PSA*	*S. malto*	*H. flu*	*NA*	*NA*	*NA*
	Culture	*S. aureus*	*PSA*	*S. malto*	*H. flu / A. baumanii* complex	—	—	—
Edin[d]	BioFire	*H. flu*	*S. aureus*	*S. pneumo*	*PSA*	*RV/EV*	*Adeno*	*PIV*
Monard[e]	BioFire	*S. aureus*	*H. flu/E. coli*		*PSA*	—	—	—

a. Murphy CN, et al. *J Clin Microbiol*. 2020;58:e00128-20; b. Webber DM, et al. *J Clin Microbiol*. 2020;58:e00343-20; c. Collins ME, et al. *J Clin Microbiol*. 2020;58:e02013-19; d. Edin A, et al. *Infect Dis*. 2020;52:479-488; e. Monard C, et al. *Crit Care*. 2020;24:434.

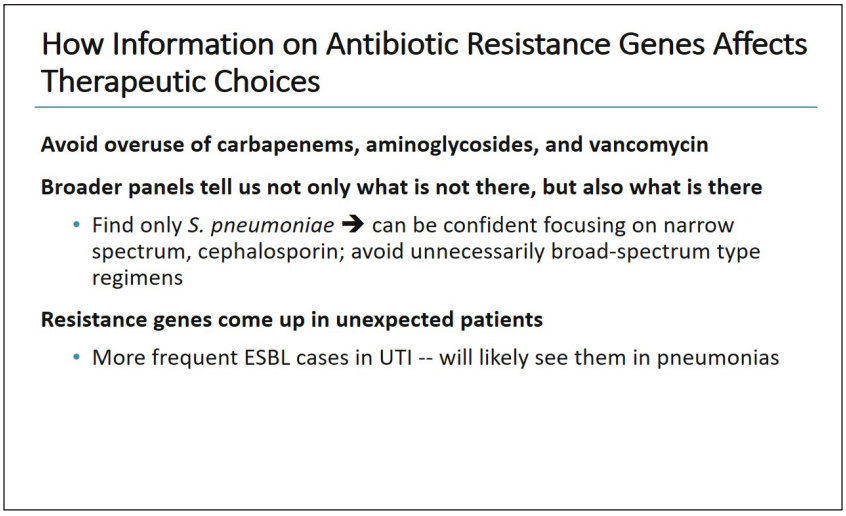
Most Common Organisms Detected in Lower Respiratory Tract Samples

Dr Burnham: Amy, I know that the both of us have been involved in studies looking at the performance of these panels. Can you tell us a little bit about some of the major studies that have been conducted to date to evaluate the impact of these newer tests?

Dr Leber: I was involved in the FilmArray pneumonia panel. On the table we're looking at, that was the largest trial today and it supported the FDA clearance. The other studies, I show you in this table, what the molecular test of comparison was, and what you notice right away is the number one pathogen in almost all of these is staph aureus, followed by H. flu or pseudomonas. Greg can maybe comment on this, but certainly there is a lot of staph aureus were isolating in a context where maybe we weren't used to seeing that much in culture and while they do match up with culture, we'll see in a moment that there are more detections that will require the clinician to make some decisions. And Greg, I can imagine that's going to be a little difficult.

Dr Moran: Right. A couple of points, as you say, staph aureus comes up a lot here as the number one. Staph aureus used to not really be on the radar for community acquired pneumonia. It's still not the most common pathogen in community acquired pneumonia, which is still strep pneumoniae. But it actually has, in more recent years, we're recognizing it more and more even in community acquired pneumonia. I think it comes up here because a lot of these studies that were done with these rapid tests, they were kind of skewed toward sicker patients. Many of them are hospital acquired pneumonias, even ventilator acquired pneumonias, a lot of them are BAL specimens, not sputum specimen. That probably skews it a little bit towards seeing more staph aureus and pseudomonas and things like that that are coming up on the list compared to if you were just looking at a community acquired pneumonia population.

But I do think that these tests are especially useful in those patients who are at higher risk for some of these resistant gram-negative bugs and things like MRSA, I think that is actually where they're probably the most valuable.

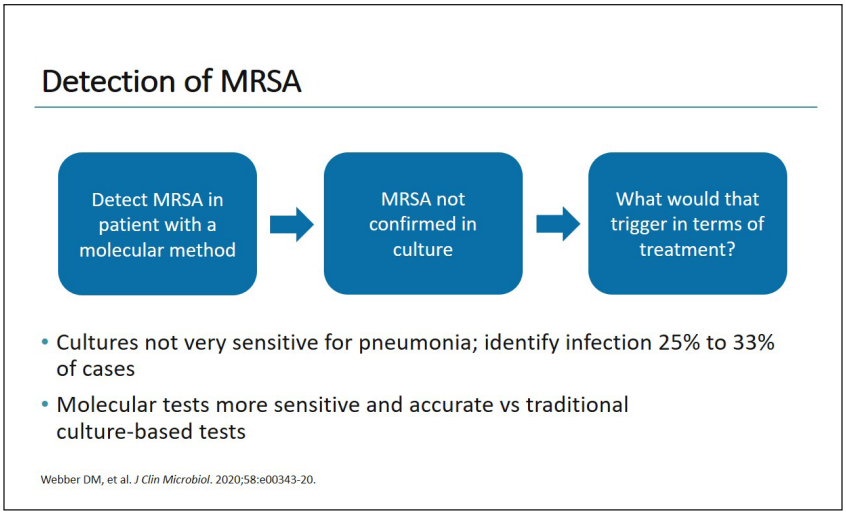


How Information on Antibiotic Resistance Genes Affects Therapeutic Choices

Dr Burnham: Thank you so much. We've spent a lot of time now talking about detecting the bacteria and the utility of that. Greg, how do you think the information about the antibiotic resistance genes might impact your therapeutic choices?

Dr Moran: I think that will be important to know because, once again, in the emergency department and in fact, even the hospital is sometimes days into this, we're still kind of shooting in the dark and we're again playing the probability game trying to say, "Well, okay, what are the most likely pathogens?" We don't want to miss anything for the sicker patients, and yet you can go crazy. You can, if you really want to make sure that you cover everything all the time, then we're going to be putting everybody on carbapenems and aminoglycosides and vancomycin. You could really go crazy and go overboard with way bigger guns than we need to do for most of these patients. It will be very helpful to know if we do or do not see some of these resistance genes.

Dr Moran: But it's not just what we find on there, it's not just that we know there is not a resistance gene, for example, that we don't see. What's also very helpful is when we have one of these broader panels, it tells us not only what there isn't, but it can also tell us what is there. For example, if we don't see any of these resistance genes, if we don't see gram negative bugs, pseudomonas, those kind of things. We know it does identify something like strep pneumonia, for example. Strep pneumonia can make people very, very sick, critically ill in the intensive care unit. And yet when we identify it, and we don't find other things, we know we can be very confident that we can focus on much more narrow spectrum, cephalosporin for example, something like that, and really avoid a lot of these very unnecessarily broad spectrum type regimens. It can be very helpful. And at the same time when we do find them, that can be critical, because occasionally they come up in patients that we may not suspect them before. We are seeing more and more ESBL cases, even in the community, we're seeing them in UTI, certainly. I think we will likely be seeing them in pneumonias and other type of syndromic infections as well.



Detection of Methicillin Resistance in S. Aureus (MRSA)

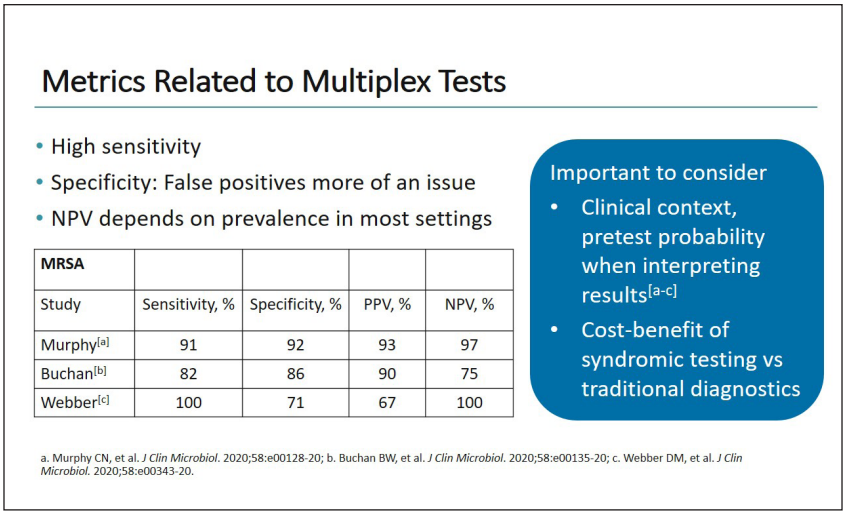
Dr Burnham: That's really important for us to think about. I can't help myself but switching back to staph aureus again. I like to say it's the pathogen that keeps our laboratory in business. Let's talk about the detection of methicillin resistance in staph aureus specifically. And Amy, going back to your study and some others, what did we learn about detection of mecA mediated, methicillin resistance?

Dr Leber: What's dramatic in looking at cumulative data, particularly for staph aureus is, if we look at the overall detection rate with molecular methods, we can see in most studies there is equal, if not greater, detection by a molecular method that's negative by culture. That is going to be really felt, I think by the clinician, obviously, of course, you're going to interpret it in the context of what else is detected and everything, but certainly the clinician will have to deal with a lot more staph aureus detections. If we look at that from the perspective of MRSA MSSA, will obviously if it grows, we can have an isolate to correlate the results and that data, if you look at it, looks fairly good in that the MRSA calls are fairly reliable. But I wonder, Greg, how will you deal with this? For example, if you had a patient where you detected MRSA from a molecular method, but it didn't confirm in culture, what would that trigger in you in terms of treatment?

Dr Moran: We know historically cultures are not very sensitive for pneumonia. I mean, historically looking back for decades of studies where they've looked at this, even in people sick enough to be in the hospital with community acquired pneumonia, you only identify a bug, maybe a quarter of the time, a third of the time. We know most cases of pneumonia admitted to the hospital, we never get the bug. And we know that these molecular based tests are far more sensitive compared to the traditional culture-based tests. When they were initially studying these new technologies, typically when there's a new test, you're comparing it to a gold standard. But actually these PCR and molecular based tests actually turned out to be better than the gold standard. They're actually more sensitive than the gold standard. We did find that we were finding a lot more positive tests on these and when we have the discrepancies with negative culture and finding MRSA, or even MSSA on one of the molecular tests or even another pathogen, when they would retest it and try to confirm with independent means the molecular-based test was actually more accurate and specifically more sensitive than the cultures.

I think we would trust it, if we had an MRSA that we identified on one of these molecular rapid diagnostic tests, then absolutely. If the patient is sick and has compatible clinical symptoms, we would absolutely want to be covering them for MRSA. And that is worthwhile information. MRSA is one of those bugs that, even though historically we would only worry about it in nosocomial infections, we absolutely are seeing a MRSA infections coming from the community. It can be a cause of community acquired pneumonia.

Dr Leber: Just to round that out, there's a study that Carey-Ann did at her institution using the pneumonia panel. We're looking at this table where they looked at standard aerobic culture versus the molecular method. Again, we see it detects more staph aureus than culture. Also the interesting is MRSA is more likely detected in a molecular, where it will be MSSA in culture. And that may not be really a discrepancy. It may represent a mixture of MRSA and MSSA in a culture in the molecular method is able to pick up that smaller population. It really does have increased sensitivity and we may learn to use it and trust it, as you've said Greg. I think that's a great point.

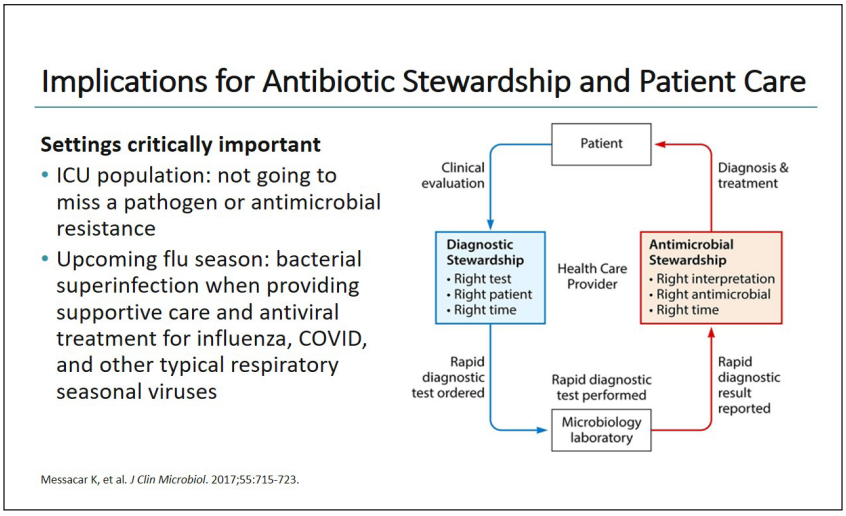


Metrics Related to Multiplex Tests

Dr Moran: I think that is very helpful. Also, we know that the sensitivity of these tests is pretty high. If you wonder, "Okay, well, can we confidently exclude an MRSA infection from these?" We know that the sensitivity of the molecular test is very high, when you're looking at sensitivity compared to other gold standards of retesting, it's in the 90 high, 90%-96% range in this study that we were looking at here. But remember that what we're looking at in the population is the negative predictive value. In particular for community acquired pneumonia, yes, it's out there, but it's a relatively small proportion. If we have a negative test, then your negative predictive value, depending on what your prevalence is in almost all settings in the United States, the negative predictive value of that test is going to be extremely high, probably 99% plus, just given the prevalence in the population. Now, maybe a little less predictive in a hospital, acquired ventilator associated pneumonia type situation, but even then, still the negative predictive value is going to be high enough. In most cases, we're going to be able to rely on that.

Dr Burnham: That's a great, great point. We need to make sure we're treating our patient and not just the lab test and considering the pretest probability when we interpret our results.

Dr Moran: Right.



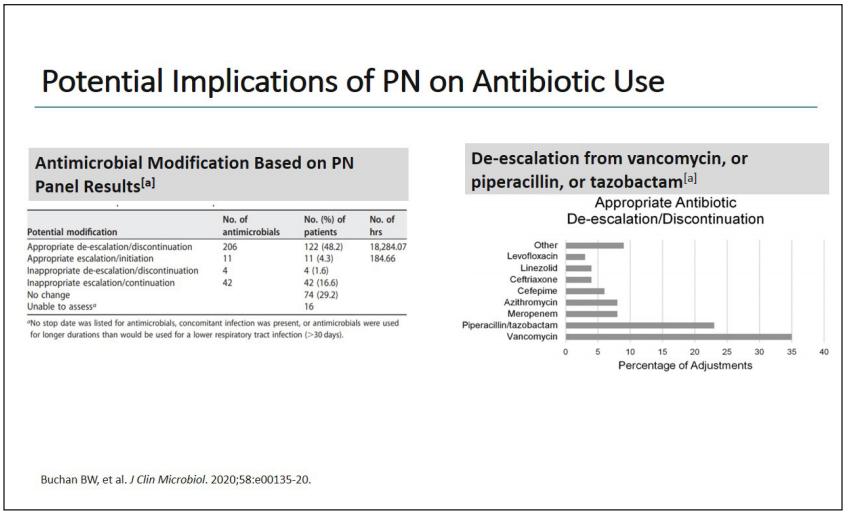
Implications for Antibiotic Stewardship and Overall Patient Care

Dr Burnham: That was a really terrific discussion of the tests and how they work. Let's switch gears just a little bit and focus more on how we actually put these into practice and the implications for antibiotic stewardship and overall patient care. Greg, considering that, how and when would you actually deploy one of these rapid multiplex tests to improve antimicrobial stewardship?

Dr Moran: Again, we kind of touched on this a little bit, probably not so much in the outpatient setting. I mean, I think we have antibiotics that we are reasonably confident will be effective in the outpatient setting. Also with the patients that are less sick, we're not quite as compelled to make 100% certain that we're going to cover every pathogen that has a very small probability of being there. And probably even so for the kind of routine community acquired pneumonia case, maybe they need to be in the hospital because they're a little hypoxic, they need some supplemental oxygen or something like that. Probably not as necessary for that. We can be reasonably comfortable with our traditional kind of ceftriaxone with a macrolides or doxycycline type thing.

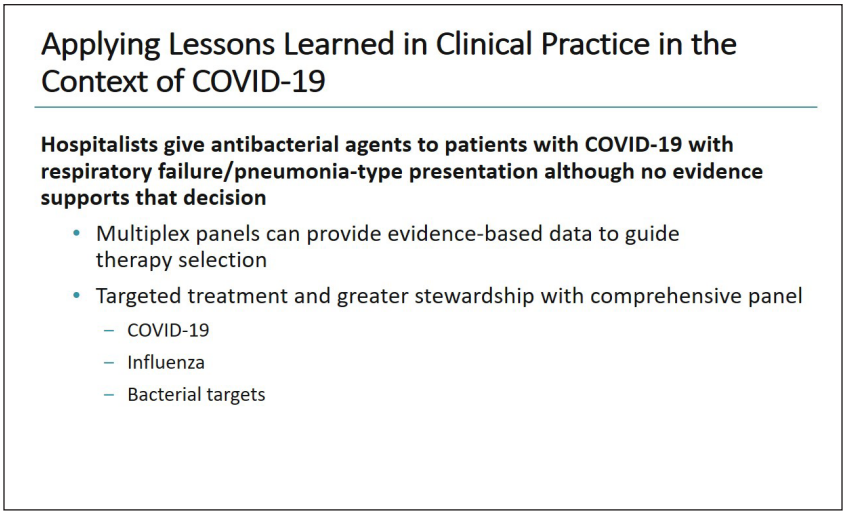
But I think a couple of settings, they will be especially and critically important, certainly in the sicker population, people sick enough to need ICU level care, where you want to be 100% certain that you're not going to miss a pathogen, that you're not going to miss an antimicrobial resistance, that you may need to address. So it's going to be especially important in that population. That's exactly the population of what we're doing now is these very broad spectrum antimicrobial regimens, that if we had a way that we could identify a pathogen, no, for example, if it is a strep pneumoniae that we don't need to worry about all these resistant things, then we wouldn't have to do that giant shotgun type approach. I think that would be an important way to do it. Also I think this is going to become increasingly important, especially in this upcoming flu season where not only going to have to worry about influenza and other respiratory typical seasonal viruses, but now we've got COVID-19 on top of all of that. That's going to be another big unknown question mark, that may be helpful to know, is there a bacterial superinfection, can we really just focus on the supportive care and the antiviral treatments if indicated, or are we going to need to give some antibacterial overage as well?

Dr Burnham: That's great. I think one of the key points you've really highlighted is to maximize antimicrobial stewardship. We also need to maximize diagnostic stewardship. By picking the right test using it on the right patients and at the right point in the clinical workflow, we can help support the goal of antimicrobial stewardship, which also means using the right anti-microbial at the right time for the right duration.



Potential Implications of Pneumonia Panel on Antibiotic Use

Some of the studies looking at the potential impact of the pneumonia panel on antibiotic use, have highlighted opportunities, for example, in de-escalation from vancomycin, something we've talked about a lot today. Or de-escalation around something like piperacillin, tazobactam.



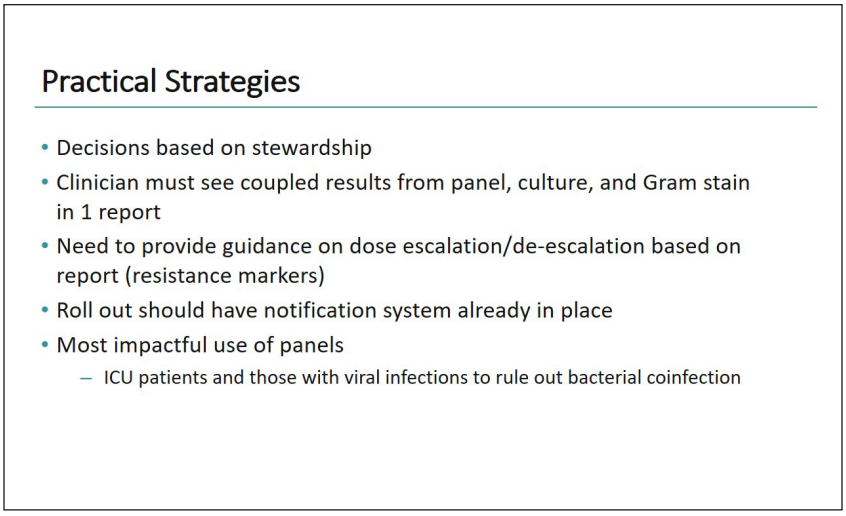
Applying Lessons Learned in Clinical Practice in the Context of COVID-19

Thinking about where we are now, all of the studies that we've talked about today were conducted before COVID-19. COVID-19 is just really new and here we are. What lessons, Greg, have you learned in clinical practice in the context of COVID-19 and how are you applying those?

Dr Moran: This is an area that's still an unknown. I mean, we really do not have an evidence basis to really make any firm recommendations as to when do we need to add antibacterial treatments for patients who test positive for COVID-19 and are coming in with respiratory failure, pneumonia type presentation. This is another area where right now I think there is a lot of practice variability. I do see most of our hospitalists giving antibacterials to patients who are sick enough to be in the hospital with COVID-19. They have a positive COVID-19 test, they've got infiltrates. I think it still makes our hospitalists nervous to not give them antibacterial antibiotics. I do see them doing it most of the time, even though we all acknowledged maybe it's necessary, maybe it's completely useless.

I think in this setting, especially when we're dealing with a disease that we don't really know enough about, we don't have any historical basis on which to make these recommendations. I think we will learn a lot in real time by using some of these multiplex rapid diagnostic tests that I think will help us learn a little faster. Who are the ones that maybe we are finding bacterial co-infections with and who we could maybe just comfortably give, just focusing on the supportive care antiviral treatments and those types of things. I think we could really learn a lot in a shorter period of time if we are doing these in our practice in real time.

Dr Leber: And I'll just chime in, that while none of the pneumonia panels yet have a COVID target, I think that is going to come. I think as Greg said, we really don't understand yet. If we were to have a comprehensive panel with COVID with influenza, with bacterial targets, we could really be treating more targeted, more stewardship involved in that. I imagine though, if you have a patient in the ICU with COVID-19 right now, it's very hard not to give them antibiotics. I think in the laboratory, we really need to help support that. I think that these panels are a way to kind of give evidence-based data to guide therapy.



Practical Strategies

Dr Burnham: How do we really now get some practical strategies that we can share with people and how they can incorporate these into the pathway of clinical care? Well, let's start with Amy. Amy, can you share some examples from your practice that might help our learners consider how they might apply the information these tests are providing?

Dr Leber: Well, first it is what population you're going to use it on. Of the three of us, Greg's hospital is the only one actually implementing it. And they're primarily adult. As Greg mentioned, they see patients in the ED that are transferred to the ICU. But I believe Greg, that only ID is currently able to order the panels, is that correct?

Dr Moran: That's a diagnostic test stewardship practice that we have in place in my facility.

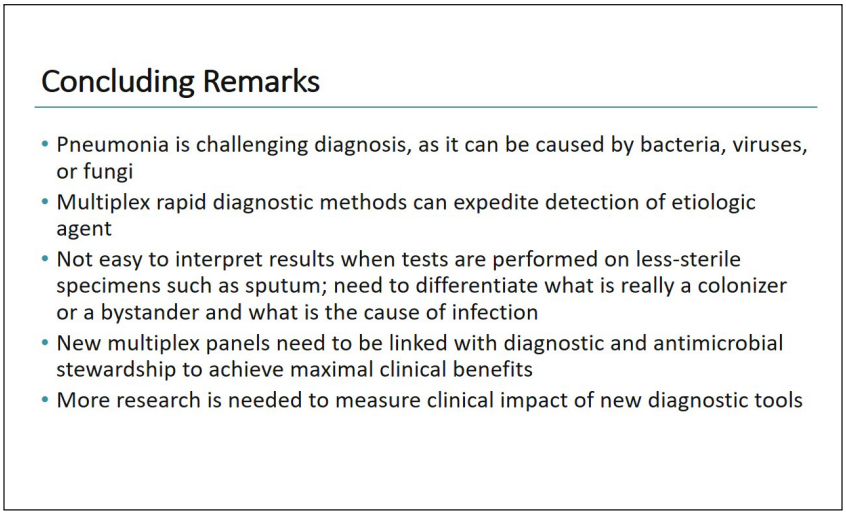
Dr Leber: I think as you roll this out, there'll have to be decisions made on a stewardship basis, who can get this test. And some of this we went through earlier, it cannot be separated from culture and gram stain. From the mechanics of reporting it, I think it's very important that we couple those results of the clinician sees them in one concise report that can be very difficult to do in a medical records EMR. That really should take some careful consideration as we roll these out. And finally report comments are going to be critical. If we're giving resistance markers and bacteria results, we need to guide them what that means in terms of escalation, de-escalation.

If we look to the examples from the literature of other multiplex panels with resistance markers, for example, the blood culture panel molecular multiplex, if you involve stewardship and any microbial oversight early and immediately, you have much more chance of having an effect on outcome. I think that rolling it out with that notification system already in place will be really important to get the most out of this test.

Dr Burnham: That's a great, point. We've already learned so much from implementation of rapid blood culture diagnostics. We don't need to reinvent the wheel. As a big fan of the gram stain myself, I'm pleased to know that, that you agree that that's something we need to keep around and incorporate into this. Greg, how about you, from your clinical perspective, can you share some examples of how we might apply the information from these tests?

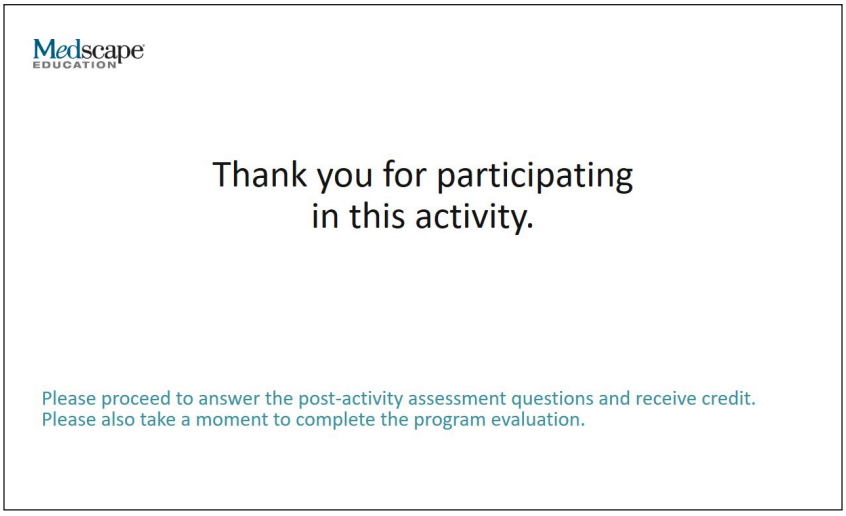
Dr Moran: I think we've already talked about a lot of the common uses that it would be. I do think the biggest and most impactful use of these tests would be in, one, those sicker patients, the ones that are ending up in the ICU, whether it's community acquired or whether it's a hospital or nursing home acquired type infection. We know that those are the ones where it makes a difference. We absolutely do not want to miss any possible pathogens. This would allow us to identify them, identify the resistance genes. Also on those patients, even if they're not critically ill, but they have a higher risk for having resistant infections. They have particular higher risk for pseudomonas, for MRSA, for other resistant gram negatives, then even if they're not so sick, we want to keep them from getting sicker, so we would like to apply an appropriate target. And those are the ones that we may not be doing the big shotgun initially right up front, but it could be helpful to identify those resistances when they're there.

Also, I think it's going to be useful for some of these sick patients with viral infections, whether it's influenza, whether it's COVID-19, because the big question there is always, is there a bacterial coinfection going on? And that drives, I think right now, a lot of unnecessary antibiotic use. I think that would be an important stewardship feature.



Concluding Remarks

Dr Burnham: That's a great point. We have a lot to learn and this new virus is teaching us things every day. Well, we've had a really detailed discussion. We've covered a lot of ground today about the diagnostic challenge that is pneumonia and that it can be caused by a bacteria, viruses and fungi. And because of this, and pure treatment is a challenge. We talked about some new multiplex rapid diagnostic methods that can expedite the detection of the etiologic agent and how challenging it might be to interpret some of the results, especially when we perform these tests on less sterile specimen, such as sputum, where we have to differentiate, what's really a colonizer or a bystander, and what's the cause of infection. We talked about the importance of linking these new laboratory methods with diagnostic and antimicrobial stewardship, so that the resources that we're putting into them relate to maximal clinical benefits and the best patient outcomes. I think we're just at the beginning of this journey, what we need now are true perspective studies to measure the clinical impact of these new tests.



Thank you

With that, Amy, Greg, I'd really like to thank you for this wonderful discussion. And I would like to thank you for participating in this activity. At this time, I ask that you please continue on to answer the questions that follow and the complete the evaluation.

Abbreviations

AST = antimicrobial susceptibility test

BAL = bronchoalveolar

ED = emergency department

ESBL = extended spectrum β-lactamase

FDA = US Food and Drug Administration

HPN = hospitalized pneumonia panel

ICU = intensive care unit

LRTI = lower respiratory tract infection

MRSA = methicillin-resistant Staphylococcus aureus

NPV = negative predictive value

PN = pneumonia panel

POC = point of care

PPV = positive predictive value

RDT = rapid diagnostic test

RTI = respiratory tract infection

UTI = urinary tract infection

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