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Rapid Pathogen Testing With PCR/ESI-MS

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The RADICAL multicentre observational study was performed to compare PCR/ESI-MS to standard microbiology in critically ill patients.

Dr. David Brealey, Consultant Intensivist at University College Hospital, London, was one of the investigators in the UK arm of this trial, and explains more about the challenges of diagnosing infections in the ICU and the potential of rapid pathogen testing PCR/ESI-MS

What are the key challenges in the diagnosis of severe infections and sepsis?

The clinical definition of sepsis is extremely vague, and many conditions can masquerade as “sepsis”. Doctors are often unable to determine when a patient’s current temperature or condition is related to an infection or some other process. They worry that they may miss an infection or a septic episode, and therefore treat the patients with antibiotics. What is unclear with the current definition of sepsis is how many of those patients treated with antibiotics do not actually have an infection, let alone sepsis. The pressure on clinicians is not to miss sepsis and to prescribe antibiotics in what is described as a “timely manner”. There are many patients getting antibiotics, who perhaps don’t need them. That exposes them to a degree of risk, and in the hospital environment the more powerful broad-spectrum antibiotics can have a significant impact on vital organ function. From the society point of view the broad-spectrum antibiotics drive multi-drug-resistant bacteria. The issue, put simply, is overuse of antibiotics by doctors, who are unsure whether the patient is truly infected or septic, because sepsis definitions are so poor and diagnostic techniques are inadequate.

Are the current methods used for the diagnosis of sepsis adequate? If not, why not?

Currently the diagnosis of sepsis is clinical, and it is backed up by blood or sputum cultures. If you treat bacterial cultures inappropriately, those bacteria are not going to thrive and divide and we are not going to detect them. Giving patients antibiotics before the cultures are taken really lowers your chance of getting any results through. At our institution and others, in the critical care environment only about 10% of blood cultures ever show a positive result. Assuming that most doctors take a blood culture because they think the patient might just be septic, only 10% come back as positive, and it takes about 48 hours for the results. 48 hours to wait for a result for someone who might actually be septic is just too long. We need to have antibiotics administered within the hour. If you compare sepsis as a medical emergency to stroke, the diagnostic process is lacking. If someone comes into hospital anywhere in Europe with a stroke, they will be rushed to a stroke centre, have a CT scan, and an immediate diagnosis and treatment will be given. What they won’t do is give you a very dangerous treatment now, not really knowing whether or not you have the condition. Diagnostics for sepsis is far behind diagnostics for other medical emergencies.

You were part of the RADICAL Study, can you briefly tell us about the main findings?

The RADICAL study was a comparison of the rapid pathogen detection technology, PCR/ ESI-MS, versus standard hospital i.e. culture techniques. The study compared this in a real world environment. If you were in a RADICAL centre, and the doctor was taking a blood culture or a culture from any other part of your body because they thought you were septic, they would also take a sample for PCR/ESI-MS. The two were directly compared.

The key finding is that PCR-ESI-MS was able to identify over three times the number of pathogens in blood compared to culture, and in about 8 hours compared to 48 hours. The hit rate for cultures was about 11%. Eleven percent of cultures found something, whereas PCR/ ESI-MS found about 33%. The other startling finding was the negative predictive value, such that if PCR/ESI-MS was unable to find something in 8 hours, you could be 97 percent sure that your cultures were also going to be negative at 72 hours. This gives you early on the confidence that probably there is no bacteria, fungus or virus there. That doesn’t mean there is no infection in the body, because you can have a localized infection that doesn’t go into the bloodstream. It may not give you the confidence to stop antibiotics, but it certainly could lend some weight in that direction. We also looked at cultures from the respiratory tract, bronchoalveaoli, which are difficult to look at, as they are colonized with a lot of different bacteria, and PCR/ESI-MS outperformed culture there and in a fraction of the time.

It was an observational trial, so we were just looking at what the results were, we were not acting on them, and the clinicians didn’t know the PCR/ESI-MS results. The trial didn’t answer what would change if the results were known, so we asked a pool of independent doctors to look at the results and the clinical case reports, and asked if they would change the way they managed the patient. 42% stated that they would have altered the patient’s management. If the PCR/ESI-MS result was positive, that went up to about 53%. Mostly they would have reduced the number of antibiotics, and leading on from that, the side effects and the exposure and pressure of multi-drug resistance, resulting in the de-

escalation of antibiotics in the hospital environment. The question of what would really happen if the clinician had the result is unanswered at the moment, and trials are being designed to discover that.

In which way do you think PCR/ESI-MS could improve antibiotic stewardship in the ICU?

The technology on its own in a lab won't make a difference. But combined with active reporting and active stewardship it could make a massive difference. The patient comes into the ED, and you think they have pneumonia – within 6-8 hours, with PCR/ESI-MS you would know if they have bacteria in their bloodstream. I would suggest what's needed is that as the result comes out so a microbiologist phones to advise on what antibiotics are needed. In hospitals it's usually the residents who prescribe antibiotics and they won't necessarily have the confidence to de-escalate antibiotics. So the speedy result need to be backed up with good stewardship and excellent communication.

What in your opinion will be the main barriers for adoption of PCR/ESI-MS?

The main barrier to hospital administrators will be cost, and obviously the business case has to be made alongside the evidence for its effectiveness. If you can prove that this technology makes a difference, reduces mortality, time on intensive care or hospital length of stay, antibiotic usage and therefore the drugs budget, that is the financial business case. The evidence for this needs to be amassed.

The other barrier is culture. Doctors need to be weaned off antibiotics as a crutch for any unknown fever. We need the diagnostics to be sure that stopping antibiotics, or not starting them in the first place is the right thing to do. The RADICAL study is a good start. We have to get that culture change going.

Can you describe for us a clinical situation where you think PCR-ESI-MS could be useful?

UCL has patients undergoing bone marrow transplants for haematological malignancies such as leukaemia. The problem is that they are immuno-suppressed. They almost invariably get a temperature after transplants, and because we cannot diagnose it immediately, they all get antibiotics. Some get better, but some persist and come to intensive care. By this point they are saturated in antibiotics, and you are unable to tell if the kidney or liver failure is the result of drug reactions or the bone marrow transplant or an infection or something else. Cultures will all be negative because the patient is saturated in antibiotics. Knowing what we are dealing with will mean cutting antibiotics out and targeting the ones we need to.

PCR/ESI-MS could make a difference when it is an emergency and inappropriate to wait 48 hours for a result. It could revolutionize the way we handle sepsis, in a way we haven't seen for decades.

Note

The technology (PCR/ESI-MS) evaluated in the RADICAL study is now commercially available as the CE-marked IRIDICA platform and assays.

See Also: Clinical Benefits of Rapid Pathogen Testing with PCR/ESI-MS

See Also: Rapid Pathogen Testing With PCR/ESI-MS In Practice

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