Procalcitonin as diagnostic biomarker of sepsis

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assesses each antigen individually and ignores potential synergies for strains that coexpress multiple antigens. The authors reported that 50% of strains expressed at least two of the 4CMenB antigens and, therefore, conclude that the coverage estimate might be conservative.

Several points merit consideration. First, the 4CMenB antigens come from protein families with high structural variability. In the study, MATS potency against factor-H-binding protein variant 1 (ie, the vaccine variant) was very high, but was low or absent for variants 2 and 3. Hypothetically, widespread vaccination might create evolutionary pressure that favours protein variants not covered by 4CMenB, similarly to the serotype switching seen after the introduction of the seven-valent pneumococcal conjugate vaccine.[9] Experience with 4CMenB is currently limited to that in short-term clinical trials[10] and, therefore, the stability of coverage is unknown. Second, MATS potency showed important regional variation within Europe, from a low of 67% in Spain to a high of 89% in Italy. The vaccine's coverage in other parts of the world has yet to be shown. Lastly, although 4CMenB aims to prevent MenB, the protein antigens are not restricted to serogroup B meningococci. Strictly speaking, 4CMenB is the world's first pan-meningococcal vaccine. Assessment of its coverage against other meningococcal serogroups (eg, serogroup X, for which as yet there is no vaccine[11]) has evident public health relevance. These questions might be answerable with MATS.

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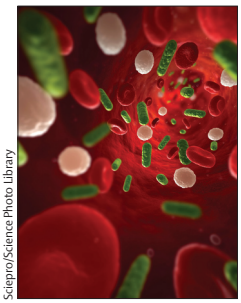
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Procalcitonin is a peptide released in response to pro-inflammatory stimuli, particularly bacteria-associated inflammatory mediators.[1] At present, procalcitonin is a biomarker for infection most used in hospitals and seems to have a higher diagnostic accuracy than other traditional biomarkers of inflammation.[2] Particularly, procalcitonin has attracted a great deal of attention as a potential means to guide antibiotic stewardship, reducing inappropriate antimicrobial use and associated resistance.[3]

Several meta-analyses have assessed procalcitonin as a marker of sepsis.[4–9] The findings of these reports conflict with regards to the association between procalcitonin and improved patient outcomes—eg, adequate treatment, mortality, or length of stay in the intensive-care unit. These discrepancies are probably a result of confounders such as treatment and population heterogeneity, diagnostic challenges related to identification of the causative pathogens, absence of a true reference standard, the complexity of sepsis, differences in assay sensitivity, and shortcomings in the methods of the studies with inadequate statistical power to detect changes for hard endpoints. In *The Lancet Infectious Diseases*, Christina Wacker and colleagues[10] add to the ongoing debate about the clinical benefit of procalcitonin as a diagnostic test for sepsis. They included more than 30 studies with 3244 patients in the overall analyses, adjusting for many potential confounders. Compared with previous reviews, this meta-analysis used more appropriate criteria for study selection, a more rigorous method, included more studies, and provides overall a more favourable

assessment of procalcitonin as a marker of sepsis, which might surprise those who are still critical about the added diagnostic value of procalcitonin.[4,5]

Despite the high quality of the methods used in the meta-analysis, several questions remain: will the findings affect day-to-day clinical decision making, ordering of additional diagnostic tests, and antibiotic prescription habits? Will procalcitonin enable early sepsis to be detected in critically ill patients?

First, procalcitonin is not a magic bullet for early detection of sepsis (there are none). Second, for many clinical situations, procalcitonin does not add crucial diagnostic information—a clinician's assessment is accurate enough to distinguish septic patients from those without signs and symptoms of severe infection.[11] For situations of greatest clinical uncertainty, procalcitonin does not offer good enough negative predictive value to justify withholding antibiotic treatment—the patient could still have potentially life-threatening sepsis, in contrast to mild-to-moderate respiratory tract infection, for which withholding antibiotics is potentially less harmful.[7–9] This shortcoming has been shown in a clinical trial in France,[12] in which critical care physicians were reluctant to trust procalcitonin measurements for making initial treatment decisions for septic patients. The doctors often disregarded the procalcitonin result and started antimicrobial treatment, despite low baseline procalcitonin concentrations. Thus, clinicians were not deterred from giving pre-emptive antibiotic treatment when they suspected early sepsis, irrespective of the availability of procalcitonin. However, procalcitonin measurements were useful for deciding whether to discontinue antibiotic treatment early.[12,13]

Third, the investigators' claim that "procalcitonin can differentiate effectively between sepsis and systemic inflammatory response syndrome of non-infectious origin" is not entirely supported by a sensitivity of 77% (95% CI 0·72–0·81), corresponding to 23% of patients not receiving adequate treatment, and a specificity of 79% (95% CI 0·74–0·84), corresponding to 21% being unnecessarily treated. As outlined by the investigators, several issues—eg, different procalcitonin assays and cutoffs for sepsis, publication bias, population heterogeneity, moderate quality of the included studies, variation in prevalence of sepsis (34–88%), and other study characteristics—could have biased the reported performance. Nevertheless, we believe that the positive likelihood ratio of 3·67 and negative likelihood ratio of 0·29 are of little use for guiding initial treatment decisions in critically ill patients with a moderate-to-high pretest probability of sepsis.

An ideal biomarker should distinguish between various stages of bacterial infection, inform further diagnostic tests, help to time treatment, and provide information about prognosis. Procalcitonin is not a perfect biomarker but it is the best available means for making individualised treatment decisions to reduce duration of antibiotic treatment or withhold antibiotics for non-life-threatening respiratory tract infections.[7–9] We anxiously await the results of further clinical trials of procalcitonin and other biomarkers of sepsis, which will hopefully improve antibiotic stewardship strategies in intensive-care units. Finally, as with any other diagnostic test, the potential risk of overuse of procalcitonin should not be ignored since it could lead to increasing expenditures (ie, assay cost, use of additional cultures), false-positive results (ie, related to trauma or surgery), and unwarranted adverse effects.

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Applying lessons from SARS to a newly identified coronavirus

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Human infection with a newly identified novel coronavirus has rapidly focused global attention on risk assessment[1–6] because its epidemic potential is not known. First detected in September, 2012, in a patient who had died of an acute respiratory illness in Saudi Arabia,[4] it was soon confirmed in a Qatari patient with a similar illness in London, UK. These cases triggered collaborations between the Kingdom of Saudi Arabia Ministry of Health (KSA-MoH), Qatar, and other global partners. The immediate need was to ensure the safety of the 3 million pilgrims attending the Hajj pilgrimage in October, 2012. Testing of pilgrims before and after Hajj 2012, and case based surveillance for the novel coronavirus during Hajj, suggested that the virus was not in circulation at the time.[7]

Continued risk assessment of the global threat of the novel coronavirus involves close collaborations between KSA-MoH, WHO, the UK Health Protection Agency (HPA), and other global partners. As of March 12, 2013, 15 patients—eight from Saudi Arabia, four from UK, one from Germany, and two from Jordan—were reported with confirmed infections, and nine of these have died. Ascertainment of the country of initial infection remains unclear and at least three cases had a history of travel to another country (including Pakistan and Egypt). Eight cases occurred in three clusters, and 13 required intensive care. In the UK cluster, three members of the same family were infected: one individual had recently travelled to Pakistan and Saudi Arabia, whereas the other two had no recent travel history,[8] suggesting person to person transmission. Although two of the cases had severe respiratory symptoms, one had mild symptoms suggesting a range of clinical expression. Contacts of the UK cases have been identified by the HPA and KSA-MoH, and follow-up tests have so far been negative for the molecular targets of the novel coronavirus.[8]

Coronaviruses are very common, and widely dispersed in animals and in human beings. They can infect the respiratory tract, gut, liver, and CNS, causing a range of illnesses. Sequence data have classified the virus as a β coronavirus similar to bat coronaviruses.[9] Not much is known about the novel coronavirus with respect to the source, mode of transmission, epidemiology, geographic distribution, predisposing factors for infection and disease, incubation period, immunopathogenesis, range of clinical manifestations, and epidemic potential.

Previous WHO guidelines for screening of the novel coronavirus were determined by travel to, or residence in, the Arabian Peninsula.[2,10,11] Although by definition these might indicate the pattern of diagnosed infections, the focus on the Middle East would have led to individuals with this viral infection in other geographical regions being missed. Latest WHO guidelines now recommend universal screening to define the epidemiology of this novel coronavirus.[12]

Available molecular tests for detection of active cases of infection and screening of contacts are experimental and their sensitivity and specificity require definition. Serological tests for the novel coronavirus are urgently needed for accurate assessment of infection in asymptomatic contacts and for large-scale serosurveys to improve understanding of the epidemiology and global geographical distribution of this virus. Validated standard treatment protocols and case investigation forms are also needed. Findings of controlled studies of cases and contacts could provide information that leads to the source of infection.

Lessons from the severe acute respiratory syndrome (SARS) epidemic showed the importance of rapid genetic sequencing, and these have been applied for study of the novel coronavirus,[4,9] enabling effective sharing of clinical, epidemiological, and microbiological information.[2,7–13] Another lesson was that although laboratory testing is important to confirm infection, it does not replace accurate case definitions, regular updates as information