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Should “empiric” antibiotic therapy be considered old-fashioned?

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The Surviving Sepsis Campaign recommends starting empiric broad-spectrum antibiotics in the initial management of patients with severe sepsis and septic shock (Rhodes et al. 2017). As a consequence, many patients receive unnecessary antibiotics, exposing them to adverse events, while others might be undertreated in spite of broad-spectrum therapy whenever the causative bacteria carry resistance mechanisms, like extended spectrum betalactamase (ESBL) or carbapenemase enzymes (ENVIN-HELICS 2016).

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Over the last decade, automated diagnostic tests have been developed, which amplify resistance genes (Buchan and Ledeboer 2014). Some of these assays require bacterial growth in blood culture bottles to allow amplification of resistance genes, a process which may take 8 hours. Other tests may even be used as a point-of-care tool, allowing the physician to test respiratory tract exudates, wound swabs or other type of samples at the bedside for potentially resistant microorganisms (PRM). Because they provide results in approximately one hour, they convert “empiric” therapy to “directed” antibiotic treatment.

The purpose of this post is to discuss the need to implement this new approach to choose the most adequate antibiotic treatment from scratch.

The conventional procedure of identification of causative microorganisms in different culture media and their susceptibility to antibiotics over several days, has established the need to “empirically” cover for PRM in the presence of risk factors, while waiting for the definitive microbiological report. Nevertheless, this strategy fails to provide adequate treatment in around 30% of cases, according to a recent Italian publication (Viceconte et al. 2017). Another retrospective, multicentre international study found a 54.5% incidence of initial antibiotic treatment failure in healthcare-associated complicated urinary tract infections (Karve et al. 2018). Early ventilator-associated pneumonia (VAP), within 4 days of mechanical ventilation, is usually caused by normal susceptible oropharyngeal flora. A recent multicentre study showed, however, a high 50.7% prevalence of resistant microorganisms in patients without risk factors (Martin-Loeches et al. 2013), making it difficult to choose the right empiric antibiotics.

The bad news is that the likelihood of giving adequate empiric antibiotic coverage is decreasing, according to a very recent study (Daitch et al. 2018). Three prospective cohorts of 811 bacteraemic patients belonging to three time periods (1 January 1988 to 31 December 1989; 1 May 2004 to 30 November 2004; and 1 May 2010 to 30 April 2011) were included. In the last period, 55.9% of patients received inappropriate empirical treatment, compared to 34.5% and 33.5% in the first and second periods, respectively, a significant upward trend (p=0.001). Inappropriate empiric treatment, in turn, leads to increased mortality, length of stay and costs (Zilberberg et al. 2017).

Inadequate empiric treatment for at least 2 days in 30% of bacteraemic patients while waiting for results of the classical culture methods, considering that new diagnostic assays are able to detect resistance genes in around 8 hours, is unacceptable. It is time to demand the implementation of the routine availability of the new molecular tests, in order to abandon “empiric” and implement “directed” antibiotic therapy.

Of course, these new rapid molecular tests only detect known resistance genes and do not substitute for the standard cultures. It will continue to be necessary to study new resistance mechanisms and pathogenic determinants to preserve the high agreement of these assays with classical

cultures (Cercenado et al. 2012) (Lepainteur et al. 2015; Rood and Li 2017; Pannala et al. 2018; Ashkenazi Hoffnung et al. 2017; Vanstone et al. 2018). Patients will only receive the antibiotic they need, and unnecessary combination therapy and their potential side effects will be avoided, particularly in the high risk severe patient populations.

An older study analysed the impact of an immediate species determination and susceptibility information on outcome in patients with blood cultures showing Gram-positive cocci in clusters (Parta et al. 2010). Early availability of results (group 1) was compared to a historical cohort with delayed reporting after traditional microbiological methods (group 2). In patients with methicillin-susceptible *S. aureus* (MSSA) bacteraemia, mean time to initiation of appropriate therapy was 5.2 hours in group 1 and 49.8 hours in group 2 (P=0.007). Six (50%) of the 12 patients in group 1 and 39 (81%) of the 48 patients in group 2 received unnecessary methicillin-resistant *S. aureus* (MRSA) coverage for MSSA bacteraemia (P=0.025). To which group would you prefer to be allocated if you happen to need antibiotic therapy for *S. aureus* bacteraemia?

Another study proved that the routine use of a *S. aureus* rapid diagnostic test in bronchoalveolar lavage (BAL) or mini-BAL samples of 328 patients with suspected VAP in a point-of-care laboratory reliably excluded the presence of MSSA and MRSA. The negative predictive values of the rapid detection test were 99.7% (98.1 to 99.9%) and 99.8% (98.7 to 99.9%) for MSSA and MRSA, respectively (Leone et al. 2013). Another study performed on endobronchial aspirate samples in VAP even demonstrated a good correlation between the cycle number for a test becoming positive (Ct) and the size of the bacterial inoculum (Burillo et al. 2016).
In patients with abdominal sepsis admitted to ICU, an observational study analysed the clinical usefulness and applicability of Xpert®Carba-R to detect carbapenem resistance compared to standard microbiological culture. When considering the only 5 mechanisms of resistance detected by both methods, the overall diagnostic performance of the rapid test was: sensitivity 100% (95% CI 69.1-100), specificity 94.2 (95% CI 80.8-99.3), PPV 83.3 (95% CI 59.6-97.9) and NPV 100% (95% CI 89.4-100) (Cortegiani et al. 2016).

To conclude, our proposal can be explained by two examples of clinical scenarios for severe infections, in which antibiotic treatment failure is not acceptable, because it is associated with increased mortality:

1. Cases where access to a representative clinical sample (respiratory, urine or exudate) is either not feasible or no particular source of infection is suspected, but blood cultures have been taken: the microbiology labs should implement one of these rapid tests in their routine work flow for positive blood cultures and report results immediately to the clinician, who should have the commitment to modify antibiotic treatment accordingly.
2. Cases of respiratory, skin and soft tissue, and urine infections: the clinician should either order or be capable of performing a rapid test to choose the best antibiotic from start of therapy

Conflict of interest

Fernando Martínez-Sagasti declares that he has no conflict of interest. Miguel Sánchez-Garcia declares that he has no conflict of interest.

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