Diagnosis of pneumonia: A shared need

Diagnóstico de la neumonía: una necesidad compartida

Pneumonia is currently one of the most common infectious diseases and the condition that causes the greatest morbidity and mortality in adults and children[1]. According to data published by the National Institute of Statistics[2], in 2019 pneumonia caused more than 9300 deaths in Spain, representing 2.24% of total deaths.

In different studies, the crude mortality rate of patients with hospital-aquired pneumonia ranges from 30% to 70%[3]. The classic series by Luna et al.[4] points to a significant decrease in the crude mortality rate from 92.2% to 37.5%, depending on whether the prescribed antibiotic treatment was adequate or inadequate. For this reason, a rapid microbiological diagnosis is essential for adequate and targeted antimicrobial treatment.

Currently, an aetiological diagnosis is not reached for 30%–50% of patients (especially in community-acquired pneumonia) and the initial treatment is totally empiric[5]. This is mainly due to the fact that many patients have been on antimicrobial treatment prior to the respiratory sample being taken, which reduces the possibility of recovering the microorganism by conventional microbiological methods (Gram stain and culture).

In addition, traditional identification and culture procedures are a slow and poorly-performing methodology that sometimes provide delayed results, leading to inadequate therapies[6].

In recent years, we have witnessed technological progress in the area of microbiological diagnosis that permits better patient management, offering more accurate and faster results. However, molecular biology technologies (currently widely used to detect respiratory viruses) for the diagnosis of bacterial pneumonia are rarely used, despite their availability[7], partly due to outdated funding models, despite the fact that their clinical impact when applied in conjnction with therapeutic optimisation programmes is high, as documented by Chastre and Fagon, demonstrating a decrease in in-hospital mortality[8]. There are solid reflections that advocate this reality where the effects obtained exceed the costs generated[9].

To apply these new rapid molecular syndromic diagnosis technologies in the field of pneumonia, five actions would need to be promoted:

- Update overall guidelines and hospital protocols with ASPs (antibiotic stewardship programmes) and define algorithms for use and optimal treatments.
- Provide microbiology departments with the necessary technology to carry out the microbiological diagnosis of pneumonia.
- Guarantee the availability of continuous microbiological diagnosis and advice 24 h a day, seven days a week.
- Reorganise information flows to ensure the greatest clinical impact with the rapid transmission of microbiology results and their interpretation in conjunction with the application of ASPs.
- Implement funding models for these technologies according to the value they provide, taking into account that they generate very valuable information, thus enabling optimal use of health resources.

From the healthcare system manager's standpoint, a rapid test for diagnosing infectious diseases should have high sensitivity and specificity, be simple to perform and interpret, not be invasive for the patient, not require a large number of professionals or highly-complex technology, deliver high performance in a *point-of-care* model and which would make it possible to differentiate between colonisation and infection.

The implementation of rapid microbiological diagnosis strategies and protocols for hospital-acquired pneumonia based on molecular detection can be an essential aid in order to improve clinical practice in seriously ill patients, with decompensated underlying diseases, at extreme ages and in patients treated in critical units[10].

In summary, the management of patients with pneumonia must guarantee a multidisciplinary team where communication flows, and which includes clinicians, microbiologists and pharmacists in the management of the patient, with rapid microbiological diagnostic techniques available that allow the antimicrobial treatment to be adapted, since the administration of early appropriate antibiotic therapy is the main modifiable factor that improves survival.

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Antimicrobial therapeutic drug monitoring in a high-complexity neonatal intensive care unit within a paediatric antibiotic stewardship program

Monitorización de concentraciones plasmáticas de antimicrobianos en una unidad de cuidados intensivos neonatal de alta complejidad dentro de un programa de optimización de antimicrobianos pediátrico

Dear Editor:

The need for specific antibiotic stewardship programs (ASP) in children is increasingly acknowledged.[1] Neonates are a high-interest target population because of their unique characteristics and the widespread use of antibiotics in neonatal ICUs. Therapeutic drug monitoring (TDM), a key element of ASP, aims to achieve highest effectiveness with lowest risk of adverse events by maintaining plasma drug levels within a safe therapeutic range. The rapid physiologic changes as newborns mature, coexisting clinical factors, and diverse dosing regimens have led to recommendations for aminoglycoside and vancomycin TDM in this population.[2] Our paediatric ASP (PROA-NEN), formally established in 2015, includes a specific neonatal approach. This study aimed to analyze the results of amikacin and vancomycin TDM in neonates, relationships between TDM and clinical outcomes, and our physicians' adherence to local TDM guidelines.

We performed a prospective, observational study conducted in a tertiary-care neonatal ICU, including all consecutive episodes of vancomycin and/or amikacin treatment in newborns (June 2017–May 2019), excluding those lasting <48 h. Amikacin and vancomycin dosing was based on Neofax criteria (Reuters T, Montvale, USA, 2011). The current local guidelines recommend TDM in treatments lasting >3 days, and every 3 days thereafter (or 24 h after if dose is changed). Plasma amikacin was determined 8–12 h post-dose, and vancomycin pre-dose (plus 3 h post-dose in severe infection or central nervous system involvement). The therapeutic ranges were: amikacin, 1–8 μg/mL; vancomycin trough level, 5–15 μg/mL and peak 18–30 μg/mL.[3,4] Adherence to TDM guidelines was evaluated for each treatment episode and considered appropriate if at least 1 antibiotic with duration >3 days had 1 or more determinations. Statistical analyses used SAS v9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the local ethics committee for clinical research (EPA(AG)28/2017(5085)).

The study included 146 newborns: 78 (53%) males, 107 (73%) preterm, 72 (49%) with underlying diseases. There were 259 infectious episodes; neonatal late-onset sepsis was the main suspected condition (207, 80%). Infection-attributed mortality was 2.5%; renal impairment and hearing disabilities at discharge were 0.5% and 11%, respectively.

In total, 390 antibiotic courses were administered (64 amikacin alone, 64 vancomycin, 131 amikacin plus vancomycin). In total, 228 plasma determinations were performed: 132 (58%) within the therapeutic range. Non-therapeutic values led to dose changes in 93/96 cases (97%). Overall adherence to TDM guidelines was 63%: 82% for vancomycin and 30% amikacin ($p < 0.001$) (Table 1). Confirmed infection (OR 2.29 [CI 1.03–5.13]; $p < 0.04$) was the only factor related to greater TDM requests. No significant relationships were found between TDM request and infection-related mortality, clinical resolution, renal impairment, or hearing disabilities at discharge.

Therapeutic drug monitoring identified non-therapeutic antibiotic levels in 42% of determinations. Previous studies have also described significant rates of non-therapeutic levels,[5,6] although dosing schemes and TDM procedures differed from those used here. In preterm newborns, an improvement in amikacin TDM has been reported after implementing more complex dosing schemes.[7]

Regarding vancomycin TDM, a recent model-based study used AUC/MIC ≥400 as the primary pharmacokinetic target (instead of through levels, a surrogate marker), showed the need for higher vancomycin doses.[8] A multicenter clinical trial, NeoVanc (NCT02790996), is ongoing to validate new dosing regimens.

Data is scarce on adherence of prescribing physicians to paediatric TDM protocols. Some studies describe better monitoring after establishing specific guidelines, but precise data on compliance are not provided.[5,6] Pain and anemia associated with extractions are reported as barriers for TDM in newborns.[9] Although TDM enabled dose correction in many cases, a benefit on clinical outcome was not found here, likely due to the relatively low adherence to TDM guidelines and small percentage of confirmed infections. In contrast to what is reported in adults, no paediatric or neonatal studies to date have been able to demonstrate the impact of TDM on mortality or toxicity; nonetheless, expert neonatologists recommend TDM despite this lack of supporting data.[2,3] The main limitations of this study are its single-center, observational design and use of TDM procedures different from those of other studies.

To conclude, our paediatric ASP team should implement targeted actions to improve TDM requests and monitoring procedures. As a final remark, new TDM tools are emerging, such as AUC-based models for vancomycin and model-informed precision dosing (MIPD) systems, which include patient and disease information. These may be superior approaches in this scenario.[10]