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Antibiotic Resistance

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Introduction

Antimicrobial resistance (AMR) is an imminent threat to global health and has been accelerated by the inappropriate use of antimicrobials (Llor and Bjerrum 2014). Antimicrobial stewardship (AMS) is crucial to optimise patient outcomes and minimise drug toxicity and emergence of resistance (Patel and Fang 2018). Diagnostic stewardship (DS) is an essential component of AMS that entails ordering the right tests for the right patient at the right time. It also promotes the use of rapid and novel molecular diagnostic tools to allow for initiation of proper antibiotic therapy

Diagnostic Stewardship in Five Common Infectious Syndromes

This article defines diagnostic stewardship and discusses how it can be implemented in intensive care units and how it may improve patient outcomes.

while avoiding excessive use of broad-spectrum antibiotics when not needed. Care should be taken in the interpretation of the test results to avoid overdiagnosis, and unnecessary costs (Patel and Fang 2018). Despite promising results, rapid diagnostics are limited by cost, accessibility, and misinterpretation. DS relies on thorough history taking and physical examination, targeted diagnostics, appropriate specimen collection, and proper interpretation of results. Additionally, multidisciplinary teams with highly trained professionals should be involved in the diagnostic pathway. We herein discuss how DS can be implemented in five common infectious syndromes frequently encountered in the intensive care units (ICU).

1. Hospital-Acquired and Ventilator-Associated Pneumonia

Ventilator-Associated Pneumonia (VAP) is a leading cause of death in the ICU (Torres et al. 2017; Melsen et al. 2013). However, it may be hard to differentiate colonisation from infection. In addition, given the accessibility of respiratory sampling in intubated patients, clinicians tend to request many respiratory cultures and risk misinterpreting them as infections (Kena et al. 2022; Nussenblatt et al. 2014; Morgan et al. 2017). In fact, up to 50% of patients treated with antibiotics for VAP in the ICU may just be colonised (Swoboda et al. 2006). On the other hand, a delay in initiating antibiotic therapy for VAP is correlated with greater mortality (Fowler et al. 2003). Recent studies suggest that microbiological identification prior to

treatment initiation is desirable in patients who are not septic and may reduce emergence of resistance (Le Terrier et al. 2021). The Infectious Diseases Society of America (IDSA) recommends the use of both clinical and microbiological criteria to diagnose VAP, with re-evaluation occurring no later than 48 hours after starting antimicrobials (IDSA 2005).

Long turnaround times of conventional methods may delay targeted antimicrobial therapy. In a retrospective study conducted in an ICU in France during the COVID-19 pandemic, a rapid microbiological diagnostic test based on the Nested Multiplex Polymerase Chain Reaction (mPCR) method was used on protected telescopic catheter (PTC) specimens. This semi-quantitative test allows detection of 15 bacteria, 3 atypical bacteria, 9 viruses, and 7 antibiotic resistance genes within 1.5 hours of sample collection. This study showed that mPCR performed well on PTC samples with a sensitivity of 93%, a specificity of 99%, and a negative predictive value (NPV) of 100% (Razazi et al. 2022). In another retrospective multicentre study, respiratory samples were simultaneously tested using conventional microbiological methods and the new syndromic rapid multiplex PCR test (rm-PCR). The syndromic rm-PCR detected 83% of episodes of infections compared to 60% in conventional cultures and allowed treatment escalation/de-escalation in 77% of pneumonia cases (Monard et al. 2020). In another study, a multidisciplinary expert panel analysed 95 samples and simulated the changes they would have made had the mPCR been available. It concluded that

mPCR improved empirical therapy, reduced the use of broad-spectrum antimicrobials, and even diagnosed two cases of unexpected severe legionellosis (Peiffer-Smadja et al. 2020).

The INHALE WP1 study is a multicentre study evaluating two mPCR platforms for rapid microbiological screening of critically ill patients with Hospital-Acquired Pneumonia (HAP) in 15 ICUs in the U.K. Both systems were significantly faster and detected more pathogens than regular microbiology tests. Importantly, PCR detects additional organisms and could improve microbiological diagnosis of pneumonia. Bayesian latent class analysis (BLC) showed low sensitivity for routine microbiological analysis, and a higher specificity and PPV of the PCR tests when compared to routine microbiological analysis (Enne et al. 2022). Moreover, although PCR did not provide a complete susceptibility profile, it was a rapid and sensitive predictor of critical resistance that had infection control implications (Enne et al. 2022). Currently, a randomised controlled trial is exploring the potential benefits of mPCR in guiding treatment of HAP/VAP in ICU patients (High et al. 2021).

2. Central Nervous System Infections

Central nervous system (CNS) infections are associated with a very high mortality rate (Giovane and Lavender 2018). Clinical presentation cannot often differentiate a bacterial from a viral cause. It is recommended to initiate empiric treatment if microbiological identification is delayed (van de Beek et al. 2016). Additionally, clinical assessment may be inconclusive in critically ill patients (Greenberg 2008). Thus, the use of rapid and precise diagnostic tools may reduce the time to initiate appropriate treatment and avoid unnecessary antimicrobials. Microarray PCR testing of cerebrospinal fluid (CSF) is a promising diagnostic tool. Not only it is capable of detecting organisms that are present in small loads, but it also has an accuracy of 90% and a short turnaround time of one hour (Tansarli and Chapin 2020). Microarray testing of CSF is particularly useful in paediatric patients where CNS infections

can occur in the setting of normal CSF findings (Acuña et al. 2022). Nonetheless, such highly sensitive diagnostic tools may result in overdiagnosis especially if the pre-test probability is low (Moffa et al. 2020). In the absence of guidelines, DS interventions are essential to help clinicians with the proper use of advanced diagnostic tools to reduce overdiagnosis and unnecessary treatment (Goodlet et al. 2021).

Diagnostic algorithms orient clinicians and are successful at reducing excessive microarray PCR testing (Messacar et al. 2022). For instance, Broadhurst et al. (2020) reported that diagnostic algorithms avoided 75% of false-positive results without

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producing false-negatives. In many cases, the absence of pleocytosis should discourage clinicians from ordering molecular diagnostics. In fact, except in immunocompromised patients and children less than 6 months of age, CSF WBC has a high NPV of 98-100% and rules out CNS infection (Broadhurst et al. 2020). Commonly, management is often influenced by physicians' hesitancy to undertreat, especially in the ICU. This is evidenced by a study where 78% of patients with suspected CNS infection and a negative microarray result were maintained on antimicrobials (Barry et al. 2021; Dack et al. 2019). Used wisely, high-yield diagnostic tests significantly reduce time to adequate treatment and duration of IV antimicrobial therapy (Messacar et al. 2022).

3. *Clostridioides difficile* Infection

Clostridioides difficile infection (CDI) is very common among ICU patients receiving antimicrobial therapy (Dubberke and Wertheimer 2009). Nonetheless, up to 50% of patients with a positive nucleic acid amplification test (NAAT) are colonised rather than infected (Buckel et al.

2015; Polage et al. 2015). The adoption of highly sensitive NAAT instead of antigen or toxin-based assays increase the risk of over diagnosing CDI (Madden et al. 2018; Bartsch et al. 2015; Leffler and Lamont 2015; Crobach et al. 2016). Additionally, the absence of specific biologic markers for CDI further complicates the diagnosis (McDonald et al. 2018).

"Soft stops" that are integrated into the electronic health system (EHS), such as reminders to check for laxative use, can facilitate decision making for clinicians and improve test appropriateness (Quan et al. 2018; White et al. 2017). Otherwise, strict interventions called "hard stops" where orders are blocked in the absence of prespecified criteria may reduce excessive testing by up to 56% (Quan et al. 2018; Mizusawa et al. 2019; White et al. 2017). Moreover, oral vancomycin prescriptions were reduced in one study, after the implementation of a preauthorisation protocol for CDI testing (Christensen et al. 2019). When collecting samples, stool cultures should be collected in a clean container, kept at room temperature, and transported within two hours. Besides, the microbiology laboratory plays an essential role in promoting DS. For example, rejecting non-loose stools has reduced testing by 43% and CDI events by 60% (Brecher et al. 2013). Sample rejection according to prespecified clinical criteria has also helped reduce unnecessary CDI testing without influencing mortality (Truong et al. 2017). Although negative toxin testing may predict a less severe course of illness, clinicians should be aware that toxin-based testing may not have enough NPV to rule out CDI (Planche et al. 2013).

4. Bloodstream Infection

Excessive blood cultures (BC) orders are common in ICU patients with vascular and indwelling catheters who are at high risk for bloodstream infections (BSI) (Hugonnet et al. 2004). BC are often driven by leucocytosis and fever despite limited correlation (Fabre et al. 2020b). In fact, a recent review reported that up to 20% of positive BC may be contaminated (Doern et al. 2019). Contaminated BC

increase antimicrobial exposure, costs, and hospitalisation duration (Bates et al. 1990; Doern et al. 2019). When BC are unlikely to change the management in a patient with a clear site of infection and without sepsis or septic shock, they should not be obtained (Fabre et al. 2020b). However, in the presence of syndromes that are likely to yield positive BC like CNS infections, septic arthritis, and endovascular infections, or when sampling of the primary site of infection is difficult, BC could be of great value (Fabre et al. 2020b). The DISTRIBUTE study aimed to optimise BC practices by implementing an evidence-based algorithm for BC indications and education and feedback to providers about BC rates and appropriateness. It showed that these interventions effectively and safely reduce unnecessary BC (Fabre et al. 2020a). A machine learning model used in a multicentre validation prospective study showed that this model can safely withhold BC analyses in at least 30% of patients presenting to the ED (Schinkel et al. 2022).

BC should be sampled before initiating antibiotics while adhering to strict hygiene measures (Rhodes et al. 2017; Murphy et al. 2014). DS bundles (including an informational video, a standard operating procedure, and ready-to-use paper crates with three culture sets) may also improve outcomes and optimise BC diagnostics (Walker et al. 2022).

Conventional BC have a long turnaround time compared to novel diagnostics and can lead to inappropriate antimicrobial use (MacBrayne et al. 2021). Matrix-assisted laser desorption/ionisation time-of-flight mass systems (MALDI-TOF MS) is used for rapid microbial identification, characterisation, and typing. However, it may better detect gram-negative than gram-positive bacteria. Routine application of this technique, which may also reduce the mortality of bacteraemia, can further advance AMS (Yuan et al. 2020). A randomised controlled trial evaluating outcomes associated with rm-PCR detection of bacteria, fungi, and resistance genes directly from positive BC found a reduction in the use of broad-

spectrum antibiotics but without affecting mortality, length of stay, or cost (Banerjee et al. 2015). Another emerging diagnostic tool is next generation sequencing (NGS), an easy-to-use, culture-free, PCR-based diagnostic method that seems to have promising results (Sabat et al. 2017). Further studies are needed to better understand the cost effectiveness, impact on patient outcome and role in the management of novel diagnostic tools for BSIs.

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5. Urinary Tract Infection

High pre-test probability of urinary tract infection (UTI) should be the main driver for requesting urine culture (UC) orders. However, UC are frequently ordered in the absence of symptoms, or when ambiguous symptoms are present, which may lead to overdiagnosis and inappropriate antibiotic initiation. Additionally, the yield of UC may be compromised by improper sampling, contamination, or misinterpretation. Clinicians should be aware that catheter-associated bacteriuria is common and often indicates colonisation rather than infection (Nicolle et al. 2005). Hence, the IDSA's 2019 clinical practice guidelines strongly recommend against UC screening in patients with indwelling catheters (Nicolle et al. 2019) and only to obtain UC from febrile patients who are at high risk for invasive infections (renal transplant, recent genitourinary surgery, neutropenic patients, or evidence of obstruction).

To reduce unnecessary UC orders, numerous institutions have integrated computerised physician order entry and clinical decision support alerts in the electronic health systems (EHS) which are automatically generated whenever a urinalysis, UC, or

antibiotics commonly prescribed for UTIs are ordered (Keller et al. 2018). These strategies are optimised when combined with educational support on AMS and infectious disease specialist guidance. For example, Shirley et al. (2017) reported 34% fewer UC orders for catheterised patients after including readily accessible guidelines in the EHS and requiring an indication when requesting a UC. Similarly, a neuro-ICU reported a significant reduction in catheter-associated UTI when nurses reviewed UC orders with critical care physicians for patients who did not meet predetermined criteria (Page et al. 2020).

Only allowing UC when urinalysis (UA) meets pre-specified criteria, called reflex UC, has been shown to significantly reduce unnecessary cultures. The presence of pyuria on UA is the most important trigger for reflex UC and has a NPV of more than 90% (Jones et al. 2014; Richards et al. 2019; Fok et al. 2010). Other used indicators can be positive leukocyte esterase, positive nitrite, or >5-10 WBC/HPF (Howard-Anderson et al. 2020). The presence of epithelial cells may indicate that the sample was incorrectly collected and contaminated with skin flora and must prompt physicians to reconsider proceeding with UC (Ling et al. 2020).

Systemic biomarkers such as CRP and procalcitonin were shown to have poor or limited role in DS strategies in UTIs (Covino et al. 2020; Drozdov et al. 2015; Stalenhoef et al. 2019). Other biomarkers such as urinary myeloperoxidase, adenosine-5-triphosphate and urinary xanthine oxidase have too little sensitivity and specificity to be recommended (Gill et al. 2015; Fritzenwanker et al. 2016). Novel diagnostic tools such as flow cytometry (Fritzenwanker et al. 2016), MALDI-TOF-MS and the combination of both (Wang et al. 2013) have also been attempted but are limited by availability and costs.

Conclusion

Recent advances in AMS strategies aim to guide better patient care and enhance clinical outcomes while reducing unnecessary antimicrobial exposure. DS is essential for better implementation of stewardship

activities. DS include diagnostic strategies for testing based on pre-set algorithms and including novel diagnostic tools in the work-up of patients. Despite some limitations and cost, these novel diagnostic technologies have been shown to contribute to the appropriate use of antimicrobials in various clinical syndromes. Unfortunately,

novel molecular tests are not available in many middle and low-income countries. A global collaboration between all stakeholders including pharmaceutical companies, governmental, and societal organisations is essential to bring new technology to better use worldwide. In addition, in the hospital setting, a close collaboration between

infectious disease specialists, critical care physicians and microbiologists is a must to optimise the care of ICU patients and provide evidence-based diagnostics and management.

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Conflict of Interest

None. ■

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