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Case report

Tailoring antimicrobials in febrile neutropenia: using faster diagnostic and communication tools to improve treatment in the era of extensively resistant pathogens

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ABSTRACT

Febrile Neutropenia represents a medical emergency and the use of appropriate antimicrobial therapy is essential for a better outcome. Although being time-consuming, conventional cultures and antimicrobial susceptibility tests remain the golden standard practices for microbiology identification. Final reports are typically available within several days. Faster diagnostic tools, such as species identification trough Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) and molecular techniques might help to shorten time to diagnostic and also guide definitive therapy in this scenario. Here we present a case in which the use of a diagnostic molecular workflow combining MALDI-TOF and real-time PCR for relevant genes codifying antibiotic resistant integrated with instant communication report, led to a tailored and more appropriate treatment in a patient presenting with febrile neutropenia.

Introduction

Klebsiella pneumoniae carbapenemases (KPCs) were discovered in 1996.[1] Since then, the world has witnessed a wide spread of the β-lactamase among enterobacteriacea, especially *K. pneumoniae*. Nowadays, carbapenem resistant *K. pneumoniae* (CRKP) are endemic in certain countries such as Italy, Greece and Brazil.[2] CRKP bacteremia is associated with a delay in initiating appropriate therapy, higher mortality rate and risk of recurrent infection, especially in ICU and immunocompromised patients; mortality can be as high as 72.3% in cancer patients.[3] Colistin resistance among CRKP has also been reported recently, with the increased use of colistin (or its analogue polymyxin B) figuring as a potential cause of these phenomena.[4]

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Species identification using MALDI-TOF combined with RT-PCR for antibiotic resistance genes seems to be a feasible way to expedite the diagnosis, potentially leading to earlier appropriate therapy and avoiding valuable hours of mistreatment.[5] The use of new diagnostic tools to identify pathogens and resistance might be useful to improve treatment in hematological patients, considering the increasing resistance observed in pathogens causing bacteremia and the importance of appropriate antimicrobial therapy in this setting.[6] Even though the prevalence of CRKP has risen in many countries, treatment options remain limited. Ceftazidime-Avibactam has proven activity against isolates of CRKP that produces KPC[7] but not against other carbapenemases such as metallo-β-lactamases. In some scenarios, it might be an alternative to polymyxin B but its use has not been extensively studied in neutropenic patients.[8]

Herein we present a case of colistin-resistant CRKP bacteremia, identified by faster diagnostic methods and successfully treated with ceftazidime-avibactam.

Case report

A 48-yo male patient was admitted to the Hematology ward on February 12th. He had been previously diagnosed with acute lymphoblastic leukemia, having undergone chemotherapy according to the German Multicenter Acute Lymphoblastic Leukemia (GMALL) protocol. It was interrupted after 35 days due to toxicity and relapsing disease. During his initial treatment, the patient developed several episodes of infection, including – in chronological order – a MRSA bacteremia associated with thrombophlebitis, a proven localized fusariosis skin/soft tissue infection treated with systemic antifungal (amphotericin and voriconazole), and three episodes of CRKP bacteremia. All CRKP bacteremia episodes occurred during neutropenia and were treated with broad-spectrum antibiotics, combining polymyxin and amikacin – drugs shown to have *in vitro* activity against the isolates – with meropenem.

After the confirmation of relapsing disease, the patient was switched to another leukemia treatment and started a protocol proposed by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL). On June 1st, three days after initiating the protocol, the patient presented with febrile neutropenia; blood samples were taken at that time for culture and diagnostic work-up. Based on his previous infections, a broad regimen was started including meropenem, polymyxin B and amikacin. His central venous catheter was removed, as it was thought to be the primary source of infection.

Bacterial growth was detected nine hours after incubation. A Gram staining of the positive bottle revealed Gram-negative bacilli. Routine species identification and susceptibility testing were performed in clinical laboratories by the BD Phoenix instrument (Becton Dickinson, Microbiology Systems, Cockeysville, MD, USA) and manual biochemical tests.

According to an ongoing study approved by the local ethical committee, an additional sample of a positive culture bottle was delivered to the Special Laboratory of Clinical Microbiology for further study.

The protocol was developed to evaluate the performance of faster species identification by MALDI-TOF mass spectrometry using clinical samples combined with a multiplex real-time Polymerase Chain Reaction (RT-PCR) for genes correlated with antimicrobial resistance. The gene panel included epidemiological relevant genes at the institution. Samples identification was achieved by MALDI-TOF on the VITEK-MS system (bioMerieux, Marcy-L'Etoile, France). Positive bottles, between 8am and 17 pm from Monday to Friday, were assigned to MALDI-TOF.

Samples identified as Gram-positive bacteria were assigned for the detection of the following genes: *mec*A, *mec*C, *van*A, *van*B and *van*C. The Gram-negative samples were tested by five different panels: Panel 1 – ESBL coding genes (*bla*SHV, *bla*TEM, *bla*CTX); Panel 2 – carbapenemase-encoding genes (*bla*KPC, *bla*OXA-48, *bla*NDM, *bla*GES, *bla*IMP, *bla*VIM); Panel 3 – Metallo-beta-lactamases encoding genes (*bla*SPM, *bla*GIM, *bla*SIM); Panel 4 – 16S rDNA methyltransferases encoding genes (rmtB, rmtD, rmtG, armA).[9]

All the results provided by the LEMC were made available to the Transplant Infectious Diseases (TID) team responsible for the patient in a real-time report, delivered by the *WhatsApp*™ social media platform. The results were sent to a group comprising all TID specialists, including the doctor on call and Laboratory staff, and was developed exclusively to this protocol. Patient data and confidentiality were strictly followed abiding to the Brazilian Federal Council of Medicine recommendations regarding "the use of *WhatsApp*™ in the hospital environment".[10]

After 20 h of antibiotics, the patient was still experiencing fever and developed clinical deterioration. Species identification and susceptibility tests by the clinical laboratory had not been carried out by that time.

Twenty-four hours after the febrile neutropenia, the LEMC delivered the results of the study protocol to the ID team: *K. pneumoniae* was the identified isolate, harboring the genes *bla*KPC, *bla*TEM and rmtB.

Considering the vast previous use of antibiotics, local epidemiology, the identification of a GNB on the positive culture bottle and the clinical scenario, the patient was started on ceftazidime-avibactam and high-dose tigecycline, with the interruption of amikacin and meropenem.

Later, the clinical laboratory confirmed isolation of *K. pneumoniae*, resistant to amikacin, meropenem and polymyxin B, leading to discontinuation of polymyxin B; additional data revealed susceptibility only to tigecycline and ceftazidime-avibactam. Complete microbiology data, including species identification and susceptibility tests, were available to the ID team almost 80 h after the fever had started. Subsequent blood cultures collected three and five days after antimicrobial therapy were negative.

The patient was kept on ceftazidime–avibactam and tigecycline for 14 days, when ceftazidime–avibactam was discontinued. Tigecycline was administered for additional 10 days until full neutrophil recovery and hematological work-up showing remission of leukemia. Although the patient was kept on his chemotherapy treatment according to the GRAALL protocol, with a new episode of febrile neutropenia, he did

not show evidence of recurrent CRKP bacteremia. He later went through an allogeneic hematopoietic transplantation as a definitive therapy for leukemia. Despite a long period of neutropenia and immunosuppression, no CRKP bacteremia relapse was detected.

Conclusion

The bacterial identification using MALDI-TOF has been reported before in immunocompromised patients. Egli et al. analyzed 62 consecutive positive blood cultures in immunocompromised patients (solid organ or hematopoietic transplant recipients, or with febrile neutropenia) identified by MALDI-TOF, which yielded a shorter time to identification with high sensitivity and specificity in this scenario, although no effect on an appropriate therapy was analyzed.[11] Other studies using similar strategies have also reported shorter time to diagnosis associated with improvement in appropriate antibiotic therapy.[12,13]

The shorter time to diagnosis needs to be correlated with a real-time report to the clinical team to be translated into an effective intervention that improves antimicrobial therapy. Beganovic et al. analyzed 252 blood cultures from 239 patients and showed that the combination of MALDI-TOF with real-time antimicrobial stewardship intervention led to a shorter time for optimal antimicrobial therapy when compared to the implementation of MALDI-TOF alone.[14]

Instant communication provided by platforms such as *WhatsApp*™ could be integrated into patient care delivery, providing an efficient real-time report of critical results. Somehow, its use is already going on.

With more than one billion of daily users,[15] the use of *WhatsApp*™ went beyond person-to-person communication to become an important tool for a wide range of areas, including health care. It is already used as an interface for communication between health professionals,[16] with a good perception about its potential and benefits.[17]

Although it is an official channel at our institution for some administrative issues, *WhatsApp*™ is still not a formal tool integrated into patient care-delivery or doctors' communication. Nevertheless, it is widely adopted by doctors in Brazil[18] also and allowed by the Brazilian Federal Council of Medicine,[10] including the formation of medical groups, aiming to conduct discussions of clinical cases that require intervention of various medical specialties.

Jonhston et al. performed a prospective study using *WhatsApp*™ as a formal communication tool for the emergency surgical teams in a London hospital. It was an effective, safety interface, promoting instructive, informative, learning and administrative communication.[19] Despite its potential, availability and user-friendly interface, issues such as data integration, privacy and security must be fully understood before *WhatsApp*™ can be widely adopted into health care delivery.[20]

This case highlights the potential benefits and the viability of the use of faster diagnostic methods integrated with instant communication provided by already available digital tools to guide treatment and optimizing care delivery. It could be a valid approach on a very challenging scenario, such as febrile neutropenia in the context of extremely resistant pathogens.

Conflicts of interest

The authors declare no conflicts of interest.

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