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EDITORIAL

Multidrug-resistant bacteria in the grey shades of immunosuppression

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Multidrug-resistant bacteria (MDRB) are a significant threat in modern medicine and are responsible for many healthcare-related infections. MDRB emerge from antibiotic pressure and may spread through cross-contamination. Immunocompromised intensive care unit (ICU) patients are often perceived as particularly susceptible to acquiring MDRB [1]. However, a new prospective French multicenter cohort study by Kreitmann and colleagues is challenging this view [2]. The primary objective of this study was to investigate the association of immunosuppression with the incidence of colonisation or infection with MDR bacteria. The authors found, contrary to the study hypothesis, that immunocompromised patients had a lower incidence rate of ICU-associated colonisation and infection: the primary endpoint (colonisation or infection related to MDR bacteria, whichever first) occurred in 24.8% and 31.6% of immunocompromised and non-immunocompromised patients, respectively. Taking into account the risk exposure (i.e. the time spent in the ICU), the respective incidence rates were 20.8% [95% CI 16.4–26.4] and 27.3% [23.5–31.6] per 1000 patients-ICU days. Enterobacteriaceae accounted for 83.8% of MDRB. The difference in incidence was significant after adjustment with baseline confounders or time-dependent covariates in the ICU (invasive mechanical ventilation and antibiotic treatment). Nonetheless, it is noteworthy that the follow-up of colonisation was not continued after ICU discharge.

As antibiotic exposure was similar in both groups, the authors point to the potential effect of isolation measures and contact precautions as a plausible explanation for the result. Although direct isolation regimes have been reported to reduce the transfer of MDRB and reduce healthcare-associated infections, results have been conflicting [3]. However, all eight ICUs in this study consisted of single-bed patient rooms, so part of the barrier precautions was already in place. Despite the single-room structure, which is unusual in many countries, 271 events of MDRB colonisation or infection occurred in 217 of the included 750 patients (29%). Isolation measures were implemented for neutropenic patients in all participating ICUs, which may explain the similar cumulative incidence of MDRB colonisation/infection in the profoundly immunocompromised patients with haematological cancer and/or neutropenia compared to other causes of immunosuppression (21.3% vs 24.9 %).

MDRB are common in the hospital environment. A recent study in United States hospitals found that 29% of hospital rooms harbour MDRB, and 10% of patients had MDRB on their hands, with a high correlation between presence on hands and room surfaces [4]. Identification of MDRB-colonised patients is likely to modify the organisation of care not only in the ICU but also in the wards, creating the need for individual rooms and additional precautionary measures that increase the workload of healthcare workers. But do contact precautions work? This may depend on the level of precautions. A cluster-randomised trial where the intervention included culture-based active surveillance and expanded use of barrier precautions, compared with existing hospital practice, was ineffective in reducing the incidence of methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant Enterococci colonisation or infection in adult ICUs [5]. Improvement in hand hygiene practices has repeatedly been highlighted as the most effective safeguard against the spread of MDRB, and the World Health Organisation has adopted general guidelines to improve hand hygiene [6]. Despite this, several studies

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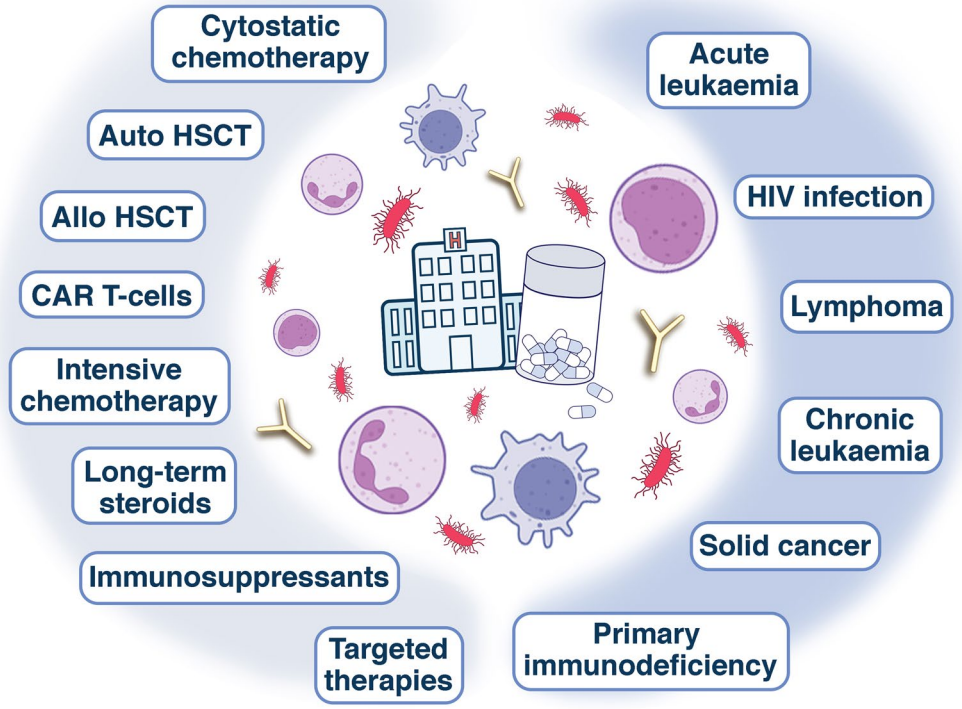

Fig. 1 Different types of immunosuppression based on underlying disease (on the right) and therapeutic management (on the left). When deciding on isolation precautions and antibiotic treatments, it is essential to consider the many grey shades of immunosuppression. *Abbreviations*: CAR: chimeric antigen receptor, HIV: Human immunodeficiency virus, HSCT: Haematopoietic stem cell transplantation, ID: Immunodeficiencies.

have found compliance in the ICU being low and among healthcare staff, physicians being the least compliant; however, this may in part be balanced by attending physicians being less likely to examine patients in contact isolation compared with patients not in contact isolation [7].

One uncertainty in Kreitmann and colleagues' study is whether the colonisation of MDRB itself may have triggered the use of more broad-spectrum antibiotics and if the lower rates of actual infection, therefore, are related to non-growth bias results. Besides, MDRB colonisation raises the question of the risk of further related infection, with the main purpose of preventing the unnecessary use of extended-spectrum antibiotics. It has been suggested that ICU-acquired colonisation with MDRB may increase the risk of ventilator-acquired pneumonia [8]. However, data from critically ill patients colonised with extended-spectrum beta-lactamase-producing Enterobacteriaceae indicate that these organisms accounted for relatively few infections (e.g. 15% of infections diagnosed at the time of ICU admission, and 10% and 27% of first and second episodes of ICU-acquired infections) [9, 10].

Importantly, as the primary objective was to investigate the association of immunosuppression with the incidence of colonisation or infection with MDRB, the underlying immunosuppressive conditions are crucial. Here, several potentially immunocompromising states were pooled into one large group consisting of patients with solid cancer within the last 5 years, active haematological malignancy, presence of neutropenia, solid-organ transplant, long-term use of steroids or other immunosuppressive drugs, human immunodeficiency virus infection or genetic immunodeficiency. This binary distribution between immunocompromised and non-immunocompromised subgroups is the main shortcoming of the study. In fact, patients with solid tumours within the last 5 years are heterogeneous, including patients with sustained complete remission and no anticancer treatment and patients with progressive/metastatic diseases and aggressive cytostatic chemotherapy or immunotherapy. Furthermore, there was significant overlap between conditions, and several patients had more than one cause of immunosuppression. Different types of immunocompromised status typically influence the degree of contact precautions and isolation regimes.

The definition of immunosuppression should not be based only on the underlying disease but also on the

stage of the disease and its therapeutic management (Fig. 1) [11]. On the other hand, many patients deemed immunocompetent harbour underlying comorbid conditions (e.g. chronic lung diseases, cirrhosis, and diabetes) that also warranted significant antibiotic pressure within the last 3 months. Furthermore, most critically ill «immunocompetent» patients exhibit numerous immune dysfunctions. They are susceptible to various ICU-acquired opportunistic bacterial, fungal, and viral infections, fulfilling the biological and clinical criteria that define immunosuppression.

Undoubtedly, patients with immunosuppression are at the highest risk of severe infections. But can all immunosuppressed patients be placed under the same umbrella? Do they all have the same risk factors? Should they all have the same spectrum of antibiotics? We believe that in order to answer these questions adequately, there is a need for an adequate classification of the type and degree of immunosuppression, which also considers local epidemiology and the patient's severity. Rather than using a black-or-white approach, we should consider the grey shades of immunosuppression.

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Declarations

Conflicts of interest
The authors declare that they have no conflict of interest.

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