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Personalised Medicine in Intensive Care

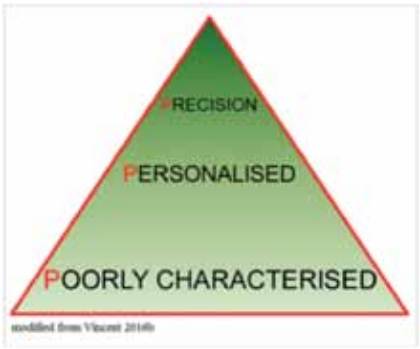
The specialty of intensive care medicine grew out of the realisation that critically ill patients needed more attention and specialised treatment than could be provided on a general ward, and that many of these patients had similar clinical problems and processes, so management would be facilitated if they were grouped together in one place. Since those early days, intensive care medicine has grown rapidly with major advances in technology and understanding of disease pathogenesis and physiology. Progress in therapeutic interventions has, however, been less marked. One of the reasons behind the lack of effective new therapies relates to problems in performing randomised clinical trials in the very heterogeneous ICU patient populations. Indeed, since the birth of intensive care medicine, we have tended to group patients with similar signs and symptoms together under "umbrella" diagnoses, such as "sepsis", "acute respiratory distress syndrome", "acute renal failure", ignoring the considerable heterogeneity within these groups in terms of individual characteristics, such as age, comorbid conditions, and genetic predisposition to disease; disease severity and degree of immune response; and individual variations in response to treatment. Performing randomised controlled trials in such mixed groups of patients will almost inevitably result in an inconclusive result as some patients in each group will respond to the therapy and others will not (Vincent 2016a).

Indeed we are increasingly aware that on the ICU, as across all other medical fields, patients must be treated as individuals and not as diseases. We have perhaps been too concerned with defining syndromes and diseases and have somewhat "forgotten" the individual people behind those conditions. We commonly hear phrases such as "he's septic", "she's a diabetic", "where's the ARDS patient?", encouraging this attitude of defining patients by their diagnoses, but we need to look behind the group label and see the individual patient so that we can select the most appropriate treatment for that person at that moment in time. This personalised approach to medicine is not new; indeed, more than 2400 years ago, Hippocrates had already noted the importance of individual characteristics in the development and progress of disease and evaluated each patient and adjusted treatment according to their "constitution, age, physique, the season of the year, and the fashion of the disease" (*Hippocrates, Nature of Man*). Basic vital signs and variations in physiological parameters, such as body temperature, heart rate and respiratory rate, have also been used for centuries to assess a patient's response to therapy. As medicine has progressed, increasingly more complex parameters have been used to predict outcome and adjust therapy, such as blood pressure and cardiac output. In another attempt to help characterise patients, biomarkers have been developed and studied as potential risk, diagnostic and prognostic indicators for various conditions, including sepsis and acute kidney injury (AKI) (McMahon and Koyner 2016; Pierrakos and Vincent 2010) although problems of specificity and availability have limited their widespread use.

> "patients must be treated as individuals and not as diseases"

These relatively non-specific and simple methods are now being complemented by more advanced techniques as, with the huge technological advances of the last decade or so, we have begun to enter a whole new era of personalised medicine. Genomic, transcriptomic, proteomic, and metabolomic profiling techniques are enabling patients' risks of disease and likely response to treatment to be more closely identified, such that the treatment(s) most likely to benefit that patient can be selected. For example, using genomic expression profiling, Wong et al. (2015) identified two subgroups of children with septic shock, one of which had increased mortality when prescribed corticosteroids. Similarly, using whole genome amplification on blood samples from patients included in the PROWESS study (Bernard et al. 2001), Man et al. (2013) identified two subgroups of patients with different responses to treatment with drotrecogin alfa (activated). The personalised medicine approach is now being applied to clinical trials, helping select more specific groups of patients who are most likely to respond to an intervention rather than the heterogeneous populations of the past. For example, a study comparing granulocyte-macrophage colony-stimulating factor (GM-CSF), an immunostimulating drug, with placebo, is currently ongoing in patients with sepsis, but enrolling only patients identified as being immunosuppressed based on their human leucocyte antigen (HLA)-DR level (clinicaltrials.gov/ct2/show/NCT02361528) Such studies will help, finally, to identify new therapies and interventions for conditions, such as sepsis, in which multiple clinical trials in heterogeneous patients groups have so far failed. Importantly, as these 'omic techniques become more widely used, costs will decrease. Drug development prices may also decrease as study populations are more carefully defined, making trials more efficient.

Hand in hand with new analytic technology has come improved informatics



capability, enabling sophisticated analysis of the large sets of patient data (demographic, physiological, laboratory and new 'omic data) being collected, aided by national and international collaborations. Simulated models are also being developed to test suggested interventions on "virtual" patients or groups of patients, informing drug development and clinical trial design. The integration of all these data into "supermodels" (Brown 2015) may ultimately enable a physician to access a personalised treatment plan for every individual. These intelligent models will be able to update and adjust recommendations automatically as new data are received.

Clearly, this is still a somewhat futuristic view of personalised medicine in the ICU. Nevertheless, as we are increasingly able to better characterise patients, our ability to identify subgroups within subgroups will increase until we reach the point at which each subgroup consists of just one patient (Gattinoni et al. 2016). This will be true precision medicine, in which medical treatments will be customised to an individual's molecular and genetic makeup. Although this approach is already being used in oncology, in the ICU environment, with the very rapid changes that occur in patient status, requiring regular treatment adjustment and thus necessitating repeated phenotypic profiling, true precision medicine is still some way off. Nevertheless, the progress from poorly characterised patient groups to personalised medicine is already a huge advance (Vincent 2016b). ■

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