*Intensive Care Med (2022) 48:1607–1610*
https://doi.org/10.1007/s00134-022-06908-6

EDITORIAL

# Personalized medicine in COVID-19

Lieke Bakkerus[1,2] and Peter Pickkers[1,2*]



Sepsis has been around since the beginning of time, continuing to have an immense impact on clinical practice as it represents the leading cause of death worldwide [1]. So far, two revolutions related to the treatment of sepsis took place: the discovery of antibiotics and the development of intensive care units (ICUs), both vastly improving the outcome of sepsis patients. Following the first consensus publication in 1992 [2], sepsis was defined as an exacerbated immune response to an infection. Consequently, pharmacological studies mainly focused on inhibiting the immune response or other sequelae of the hyperinflammatory reaction. Many trials failed to show a significant benefit from inhibiting the immune response in septic patients [3]. Progression of insight into the pathophysiology resulted in adjustments of the sepsis definition in 2016, now emphasizing the dysregulated immune response to an infection [4]. As the immune response to an infection represents a spectrum, this emphasizes the need to select and treat patients based on the underlying biological process, called 'predictive' enrichment. Since sepsis is a notorious heterogeneous syndrome, predictive enrichment is anticipated to improve treatment efficacy by selecting which patient may most likely benefit from a given therapy [5]. Nevertheless, most clinical trial designs are still based solely on 'prognostic' enrichment, where patients are selected based on the likelihood of having a disease-related clinical event that is chosen as the trial end point (Fig. 1). Likewise, following the outbreak of SARS-CoV-2, randomized controlled trials were conducted in unselected coronavirus disease 2019 (COVID-19) patients. Secondary subgroup analyses were performed based on conventional parameters such as the need for oxygen and probability of mortality, rather than based on biological processes. Nevertheless, some anti-inflammatory therapies were proven successful for COVID-19 patients, possibly because COVID-19 patients represent a more homogenous group of a hyperinflammatory phenotype [6] compared to general sepsis patients.

In this issue of Intensive Care Medicine, Fish and colleagues describe the identification of three distinguished sub-phenotypes (also called endotypes, as they are related to the pathophysiological process) in critically ill COVID-19 patients, using unsupervised analyses of 26 biomarkers within the Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial [7]. For this study, patients were either assigned to convalescent plasma or usual care. Out of the 2097 patients of REMAP-CAP, 1239 (737 convalescent plasma and 502 usual care) patients had blood drawn at baseline and were eligible for this secondary analysis. While patients had similar baseline demographic characteristics and clinical features, three sub-phenotypes emerged: sub-phenotype-1 (70% of patients), showed considerable variation of biomarker concentrations representing a dysregulated immune state and severe COVID-19. This sub-phenotype had the highest mortality, while there appeared to be therapeutic efficacy of convalescent plasma as mortality was 2.9% lower in the treatment group. Subphenotype-2 (10%) showed another, more homogeneous mixed immune response biomarker pattern. Lastly, the biomarker pattern in sub-phenotype-3 (20%) was also more homogeneous, but demonstrated a pronounced early innate immune response. Overall mortality in both subphenotype-2 and -3 was lower, and convalescent plasma appeared harmful in these patients (mortality 11.3% and 4.4% higher, respectively). In summary, biomarker determinations enabled detection of distinct sub-phenotypes in patients with similar clinical features, which are related

*Correspondence: peter.pickkers@radboudumc.nl
[1] Department of Intensive Care Medicine, Radboud University Medical Center, P.O. box 9101, 6500 HB Nijmegen, The Netherlands
Full author information is available at the end of the article

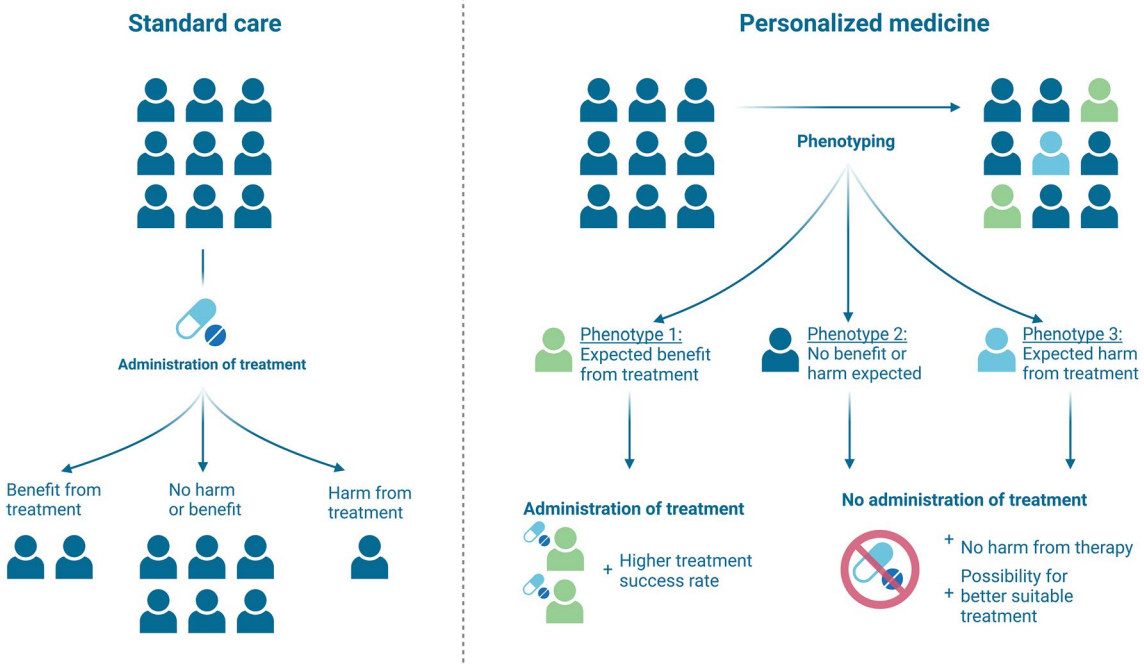


**Fig. 1** Standard care versus personalized medicine

to outcome and therapeutic efficacy of the tested therapy. The authors advocate that beneficial effects of convalescent plasma in patients with sub-phenotype-1, could be related to the activation of inflammatory pathways by low-affinity antibodies in a less inflammatory patient. This would also explain why sub-phenotype-2 and -3, being more inflammatory, may show a higher mortality after convalescent plasma administration. This study confirms the potential and importance of an enrichment strategy.

Also for therapies that are currently standard of care for COVID-19 dexamethasone and tocilizumab, predictive enrichment appears to increase therapeutic efficacy. Patients with higher pro-inflammatory biomarkers had a more pronounced improvement in survival rate following treatment with corticosteroids [8]. Similarly, probability of survival improved with tocilizumab in patients with high IL-6 levels prior to anti-IL-6 treatment, while survival was lower in patients treated with tocilizumab that had low baseline concentrations of IL-6 [9]. Another example of enrichment is selection for anti-IL1 treatment with anakinra based on the concentration of the soluble urokinase plasminogen activator receptor (suPAR). A trial using an elevated suPAR concentration as an enrollment criterion showed improved survival [10], while trials not using an enrichment strategy did not [11]. In accordance with the results of Fish et al., it is becoming increasingly clear that certain subgroups may benefit, while other subgroups may actually be harmed by the treatment. Of interest, predictive enrichment based on immunodysregulation in sepsis patients is being tested, for example in the ImmunoSep trial that is currently ongoing [12].

Beside biomarker phenotyping, other forms of phenotyping are also possible. For instance, with the use of whole blood transcriptomics, five phenotypes in COVID-19 patients emerged that could predict which patient may benefit from which therapy based on the identified pathways that were suppressed or activated [13]. Another possibility is phenotyping based on clinical parameters and conventional laboratory values. It is now becoming clear that distinct phenotypes are also present in COVID-19 patients [14], similar to the clinical phenotyping in general sepsis patients [15]. Of interest, especially the delta phenotype, representing the patients that are most inflamed, showed a significant improvement in outcome following dexamethasone therapy, while in the other three phenotype subgroups, the improvement in survival was much less pronounced.

In summary, the COVID-19 pandemic has incited an enormous amount of clinical research of which immunotherapy was shown to be effective for the first time. While most trials used some form of prognostic enrichment (e.g., based on disease severity, need for oxygen,

the likelihood to experience an event), it is now becoming clear that predictive enrichment (e.g., based on the inflammatory phenotype) is likely to further increase therapeutic efficacy of these compounds. The study of Fish and colleagues illustrates the clinical relevance and potential of predictive enrichment. Future trial design in sepsis should implement some form of predictive enrichment to increase the likelihood for beneficial effects of an intervention to emerge. Following these developments, this more personalized approach contains the promise to become the third wave of improvement of care for sepsis patients.

**Abbreviations**
ICUs: Intensive care units; COVID-19: Coronavirus disease 2019; REMAP-CAP: Randomized, embedded, multifactorial, adaptive platform trial for community-acquired pneumonia; suPAR: Soluble urokinase plasminogen activator receptor.

**Author details**
[1] Department of Intensive Care Medicine, Radboud University Medical Center, P.O. box 9101, 6500 HB Nijmegen, The Netherlands. [2] Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Nijmegen, The Netherlands.

**Author contributions**
LB was a major contributor to writing the manuscript. PP was a major contributor to writing the manuscript.

**Data availability**
Not applicable.

**Declarations**

**Conflicts of interest**
No competing interest related to this manuscript.

**Ethical approval**
Not applicable.

**Consent to participate**
Not applicable.

## Publisher's Note



Received: 12 September 2022 Accepted: 15 September 2022
Published: 10 October 2022

**References**

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet 395(10219):200–211
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. Chest 101(6):1644–1655
3. Russell JA (2006) Management of sepsis. N Engl J Med 355(16):1699–1713
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315(8):801–810
5. Pickkers P, van der Poll T (2019) What's new in immunostimulating strategies in the ICU. Intensive Care Med 45(1):110–112
6. Kox M, Frenzel T, Schouten J, van de Veerdonk FL, Koenen H, Pickkers P (2020) COVID-19 patients exhibit less pronounced immune suppression compared with bacterial septic shock patients. Crit Care 24(1):263
7. Fish M, Rynne J, Jennings A, Lam C, Lamikanra AA, Ratcliff J, Cellone-Trevelin S, Timms E, Jiriha J, Tosi I, Pramanik R, Simmonds P, Seth S, Williams J, Gordon AC, Knight J, Smith D, Whalley J, Harrison D, Rowan K, Harvala H, Klenerman P, Estcourt L, Menon DK, Roberts D, Shankar-Hari M (2022) Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized controlled trial. Intensive Care Med. https://doi.org/10.1007/s00134-022-06869-w
8. Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, He J, Thompson A, Murn M, Fountain J, Rosen A, Robbins-Juarez SY, Adan MA, Satish T, Madhavan M, Gupta A, Lyashchenko AK, Agerstrand C, Yip NH, Burkart KM, Beitler JR, Baldwin MR, Calfee CS, Brodie D, O'Donnell MR (2021) Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. Am J Respir Crit Care Med 204(11):1274–1285
9. Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, Alcaraz-Serna A, Mateu-Albero T, Rodríguez-Cortes P, Sánchez-Cerrillo I, Esparcia L, Martínez-Fleta P, López-Sanz C, Gabrie L, Del Campo Guerola L, Suárez-Fernández C, Ancochea J, Canabal A, Albert P, Rodríguez-Serrano DA, Aguilar JM, Del Arco C, de Los Santos I, García-Fraile L, de la Cámara R, Serra JM, Ramírez E, Alonso T, Landete P, Soriano JB, Martín-Gayo E, Fraile Torres A, Zurita Cruz ND, García-Vicuña R, Cardeñoso L, Sánchez-Madrid F, Alfranca A, Muñoz-Calleja C, González-Álvaro I (2021) IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. J Allergy Clin Immunol 147(1):72.e8-80.e8
10. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, Kalomenidis I, Chrysos G, Angheben A, Kainis I, Alexiou Z, Castelli F, Serino FS, Tsilika M, Bakakos P, Nicastri E, Tzavara V, Kostis E, Dagna L, Koufargyris P, Dimakou K, Savvanis S, Tzatzagou G, Chini M, Cavalli G, Bassetti M, Katrini K, Kotsis V, Tsoukalas G, Selmi C, Bliziotis I, Samarkos M, Doumas M, Ktena S, Masgala A, Papanikolaou I, Kosmidou M, Myrodia DM, Argyraki A, Cardellino CS, Koliakou K, Katsigianni EI, Rapti V, Giannitsioti E, Cingolani A, Micha S, Akinosoglou K, Liatsis-Douvitsas O, Symbardi S, Gatselis N, Mouktaroudi M, Ippolito G, Florou E, Kotsaki A, Netea MG, Eugen-Olsen J, Kyprianou M, Panagopoulos P, Dalekos GN, Giamarellos-Bourboulis EJ (2021) Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med 27(10):1752–1760
11. Khan FA, Stewart I, Fabbri L, Moss S, Robinson K, Smyth AR, Jenkins G (2021) Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19. Thorax 76(9):907–919
12. ClinicalTrials.gov (2021) Personalized immunotherapy in sepsis (ImmunoSep)
13. Aschenbrenner AC, Mouktaroudi M, Krämer B, Oestreich M, Antonakos N, Nuesch-Germano M, Gkizeli K, Bonaguro L, Reusch N, Baßler K, Saridaki M, Knoll R, Pecht T, Kapellos TS, Doulou S, Kröger C, Herbert M, Holsten L, Horne A, Gemünd ID, Rovina N, Agrawal S, Dahm K, van Uelft M, Drews A, Lenkeit L, Bruse N, Gerretsen J, Gierlich J, Becker M, Händler K, Kraut M, Theis H, Mengiste S, De Domenico E, Schulte-Schrepping J, Seep L, Raabe J, Hoffmeister C, ToVinh M, Keitel V, Rieke G, Talevi V, Skowasch D, Aziz NA, Pickkers P, van de Veerdonk FL, Netea MG, Schultze JL, Kox M, Breteler MMB, Nattermann J, Koutsoukou A, Giamarellos-Bourboulis EJ, Ulas T (2021) Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients. Genome Med 13(1):7

14. Bruse N, Kooistra EJ, Jansen A, van Amstel RBE, de Keizer NF, Kennedy JN, Seymour C, van Vught LA, Pickkers P, Kox M (2022) Clinical sepsis phenotypes in critically ill COVID-19 patients. Crit Care 26(1):244
15. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, Vodovotz Y, Weiss JC, Yealy DM, Yende S, Angus DC (2019) Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 321(20):2003–2017