The Search for Efficacious New Therapies in Sepsis Needs to Embrace Heterogeneity

The search for efficacious new therapies in sepsis needs to embrace heterogeneity.

Brendon P. Scicluna (1,2), J. Kenneth Baillie (3,4).

Affiliations:

1. Amsterdam UMC, Univ. of Amsterdam, Center for Experimental Molecular Medicine, Amsterdam Infection & Immunity, Meibergdreef 9, 1105AZ Amsterdam, Netherlands
2. Amsterdam UMC, Univ. of Amsterdam, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, 1105AZ Amsterdam, Netherlands
3. Division of Genetics and Genomics, Roslin Institute, University of Edinburgh, Easter Bush, Edinburgh EH25 9RG, UK
4. Intensive Care Unit, Royal Infirmary of Edinburgh, 54 Little France Drive, Edinburgh EH16 5SA, UK

Most new drug treatments fail because they lack efficacy[1]. In sepsis research, new therapies must contend with an additional barrier: the intractable heterogeneity of the sepsis syndrome[2]. Together, these challenges have so far proved insurmountable. Hundreds of clinical trials have been conducted, at a cost of hundreds of millions of dollars, to test new agents to modulate the host response to injury in sepsis. None has succeeded[2].

The sepsis syndrome itself is simultaneously too broad and too narrow. Sepsis encompasses numerous different aetiologies and pathophysiological processes, but - by definition[3] - excludes sterile injuries that lead to the same pathophysiology and organ failures, such as trauma, burns, haemorrhage and pancreatitis.

Some components of heterogeneity in sepsis are clinically apparent - for example, variability in causal pathogens, co-morbidities, and environmental factors and host genetics. But there is also evidence from recent studies[4,5,6] - that important pathophysiological processes that are active in sepsis patients may vary in ways that are not directly observable at the bedside. If so, there is a chance that these processes may be amenable to different treatments.

Large observational studies of blood transcriptomics applied to sepsis populations have provided several models based on molecular classification of patients with sepsis. In particular, the Genomic Advances in Sepsis (GAinS) consortium in the United Kingdom[4,6] and the Molecular diAgnosis and Risk stratification of Sepsis (MARS) consortium in the Netherlands detected distinct molecular endotypes in leukocyte genome-wide expression profiles from samples collected on ICU admission. The MARS consortium identified four molecular endotypes in all-cause sepsis (designated MARS 1-4)[6], whereas the GAinS consortium identified two molecular endotypes in community acquired pneumonia, designated as sepsis response signature (SRS) 1 and 2[4]. More recently, in an impressive demonstration of the power of open science and data sharing[7], Sweeney *et al* identified three clinical signatures - termed inflammopathic, coagulopathic and adaptive - using pooled data from publicly-available gene expression data from other studies of patients with sepsis[5]. Both the MARS and SRS molecular endotypes were associated with different mortality rates.

This is a necessary first step. But after these observations, the question remains whether the MARS/SRS signatures relate to therapeutically-targetable immunopathologies. Subgroups may reflect differing disease severity, or other features of the patients that are irrelevant to their care. Evidence of a therapeutically-relevant difference between transcriptomic subgroups among children with sepsis was provided by Hector Wong *et al* in 2014[8], but in that study, steroids were administered at physician's discretion. In order to demonstrate a treatment effect between two subgroups, it is necessary to acquire gene expression data from patients enrolled in randomised clinical trials.

For the first time, direct evidence of such an effect is reported in this issue of *AJRCCM* by David Antcliffe *et al*. Using data from the Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial[9], a generalized linear model based on a previously identified seven gene SRS classifier (DYRK2, CCNB1IP1, TDRD9, ZAP70, ARL14EP, MDC1 and ADGRE3) enabled the authors to stratify 176 patients as SRS1 (47%) or SRS2 (53%). Patients stratified in this fashion did not differ in demographics and most baseline clinical characteristics (except for rates of ischaemic heart disease). However, in line with the groups' previous findings[4], 28-day mortality in the placebo group was higher in SRS1 (37%) than in SRS2(8%)[9]. Serum lactate at baseline was also higher in SRS1. Together these observations indicate that, to some extent, SRS classification reflects disease severity.

If severity (rather than distinct pathophysiology) underlies the difference between these groups of patients, then an interaction with steroid treatment might be anticipated. There are replicated trends in large trials of steroids in sepsis and septic shock[10,11],

towards a possible treatment benefit in patients with the highest risk of death. Whether this trend is real, and if so, whether it is simply a consequence of higher event rate in this group (heterogeneity of treatment effect), are open questions at present. Based on these studies, we would have predicted a higher probability of detectable benefit from steroids among patients classified as SRS1. In fact, an interaction was detected between hydrocortisone use and SRS2-classified patients resulting in *increased* mortality estimates with adjusted odds ratio of 8.3 (95% confidence interval 1.4-47.8). That is, a signal consistent with harm from steroid treatment in the less-severe SRS2-classified group.

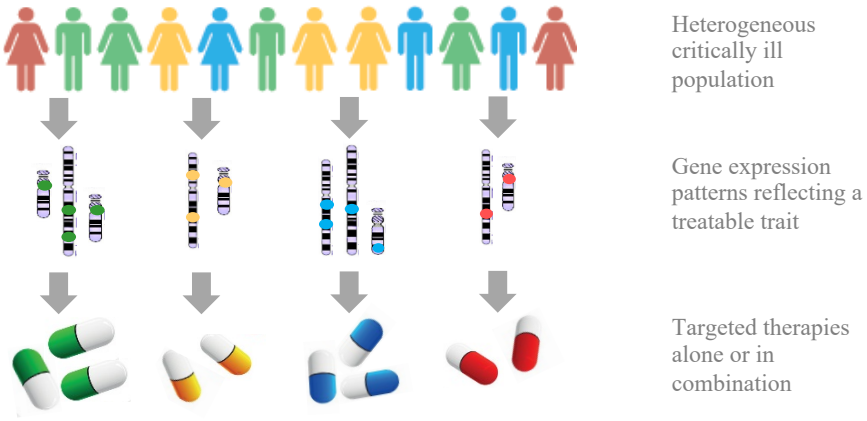

Figure 1: Diagnosis and treatment of treatable traits in a patient population.

Collectively, these results, together with therapeutic trials using sub-classifications of acute respiratory distress syndrome (ARDS)[12,13], imply that there are divergent effects from a single intervention across and in different patient endotypes, bringing them closer to the definition of a true disease endotype[14].

The investigators in the VANISH trial are to be congratulated for having the foresight to acquire transcriptomic data within a randomised controlled trial. Although confirmatory replication will be necessary, this work brings us a step closer to the primary aim of stratified medicine research: new phenotypes with direct therapeutic consequences. It is our view that future clinical trials in critical illness should consider from the outset the probability that any new therapy may have a differential effect in a subgroup of patients, and that subgroup may only be identifiable through deep phenotyping. Of the available methodologies, whole blood RNA in preservative is the most pragmatic sample to acquire to enable future enable deep phenotyping.

The dichotomy SRS1/2 classification simplifies analysis, but the groupings are drawn by bisecting what appears to be a unimodal distribution[4]. This suggests that the SRS classification reflects two extremes a continuously varying underlying biological process.

This move from the identification of subgroups to the detection of continous "treatable traits" within clinical populations has become a major focus of work in other fields[14]; we, and many others, would argue that sepsis research is in particular need of these new approaches[2]. Going further, it is very plausible that any physiological process that is active in a large proportion of patients with sepsis, will also be active in some patients with severe sterile injury. As with other therapeutic approaches in critical care medicine, new treatable traits may be generalisable across critical illness.

If the information necessary to predict response to a given therapy is present in measured clinical variables, or in the whole blood transcriptome, then detecting it becomes entirely a matter of data analysis. With current techniques, huge numbers of patients will be needed to overcome signal:noise ratios. Integration of transcriptomic signatures with genetic associations[15], may enable more efficient detection of key underlying processes. Ultimately these approaches may identify new, specific drug targets to modulate the host response to critical injury[16], and actionable estimates of individual treatment effect for critically ill patients.

References

1.Arrowsmith, J. Trial watch: Phase ii failures: 2008-2010. *Nature reviews. Drug discovery* **10**, 328–9(2011).

2.Marshall, J.C. Why have clinical trials in sepsis failed? *Trends in Molecular Medicine* **20**, 195–203(2014).

3.Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G.R., Chiche, J.-D., Coopersmith, C.M., Hotchkiss, R.S., Levy, M.M., Marshall, J.C., Martin, G.S., Opal, S.M., Rubenfeld, G.D., Poll, T. van der, Vincent, J.-L. & Angus, D.C. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* **315**, 801–10(2016).

4.Davenport, E.E., Burnham, K.L., Radhakrishnan, J., Humburg, P., Hutton, P., Mills, T.C., Rautanen, A., Gordon, A.C., Garrard, C., Hill, A.V.S., Hinds, C.J. & Knight, J.C. Genomic landscape of the individual host response and outcomes in sepsis: A prospective cohort study. *The Lancet. Respiratory medicine* **4**, 259–71(2016).

5.Sweeney, T.E., Azad, T.D., Donato, M., Haynes, W.A., Perumal, T.M., Henao, R., Bermejo-Martin, J.F., Almansa, R., Tamayo, E., Howrylak, J.A., Choi, A., Parnell, G.P., Tang, B., Nichols, M., Woods, C.W., Ginsburg, G.S., Kingsmore, S.F., Omberg, L., Mangravite, L.M., Wong, H.R., Tsalik, E.L., Langley, R.J. & Khatri, P. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. *Critical care medicine* **46**, 915–925(2018).

6.Scicluna, B.P., Vught, L.A. van, Zwinderman, A.H., Wiewel, M.A., Davenport, E.E., Burnham, K.L., Nürnberg, P., Schultz, M.J., Horn, J., Cremer, O.L., Bonten, M.J., Hinds, C.J., Wong, H.R., Knight, J.C. & Poll, T. van der Classification of patients with sepsis according to blood genomic endotype: A prospective cohort study. *The Lancet. Respiratory medicine* **5**, 816–826(2017).

7.Dunning, J.W., Merson, L., Rohde, G.G.U., Gao, Z., Semple, M.G., Tran, D., Gordon, A., Olliaro, P.L., Khoo, S.H., Bruzzone, R., Horby, P., Cobb, J.P., Longuere, K.-S., Kellam, P., Nichol, A., Brett, S., Everett, D., Walsh, T.S., Hien, T.-T., Yu, H., Zambon, M., Ruiz-Palacios, G., Lang, T., Akhvlediani, T., ISARIC Working Group 3, ISARIC Council, Hayden, F.G., Marshall, J., Webb, S., Angus, D.C., Shindo, N., van der Werf, S., Openshaw, P.J.M., Farrar, J., Carson, G. & Baillie, J.K. Open source clinical science for emerging infections. *The Lancet Infectious Diseases* **14**, 8–9(2014).

8.Wong, H.R., Cvijanovich, N.Z., Anas, N., Allen, G.L., Thomas, N.J., Bigham, M.T., Weiss, S.L., Fitzgerald, J., Checchia, P.A., Meyer, K., Shanley, T.P., Quasney, M., Hall, M., Gedeit, R., Freishtat, R.J., Nowak, J., Shekhar, R.S., Gertz, S., Dawson, E., Howard, K., Harmon, K., Beckman, E., Frank, E. & Lindsell, C.J. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *American Journal of Respiratory and Critical Care Medicine* **191**, 309–315(2015).

9.Antcliffe, D.B., Burnham, K.L., Al-Beidh, F., Santhakumaran, S., Brett, S.J., Hinds, C.J., Ashby, D., Knight, J.C. & Gordon, A.C. Transcriptomic signatures in sepsis and a differential response to steroids: From the vanish randomized trial. *American journal of respiratory and critical care medicine* (2018).doi:10.1164/rccm.201807-1419OC

10.Annane, D., Renault, A., Brun-Buisson, C., Megarbane, B., Quenot, J.-P., Siami, S., Cariou, A., Forceville, X., Schwebel, C., Martin, C., Timsit, J.-F., Misset, B., Ali Benali, M., Colin, G., Souweine, B., Asehnoune, K., Mercier, E., Chimot, L., Charpentier, C., François, B., Boulain, T., Petitpas, F., Constantin, J.-M., Dhonneur, G., Baudin, F., Combes, A., Bohé, J., Loriferne, J.-F., Amathieu, R., Cook, F., Slama, M., Leroy, O., Capellier, G., Dargent, A., Hissem, T., Maxime, V. & Bellissant, E. Hydrocortisone plus fludrocortisone for adults with septic shock. *The New England journal of medicine* **378**, 809–818(2018).

11.Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., Billot, L., Correa, M., Glass, P., Harward, M., Joyce, C., Li, Q., McArthur, C., Perner, A., Rhodes, A., Thompson, K., Webb, S. & Myburgh, J. Adjunctive glucocorticoid therapy in patients with septic shock. *The New England journal of medicine* **378**, 797–808(2018).

12.Famous, K.R., Delucchi, K., Ware, L.B., Kangelaris, K.N., Liu, K.D., Thompson, B.T. & Calfee, C.S. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *American journal of respiratory and critical care medicine* **195**, 331–338(2017).

13.Calfee, C.S., Delucchi, K., Parsons, P.E., Thompson, B.T., Ware, L.B. & Matthay, M.A. Latent Class Analysis of ARDS Subphenotypes: Analysis of Data From Two Randomized Controlled Trials. *The Lancet. Respiratory medicine* **2**, 611–620(2014).

14.Russell, C.D. & Baillie, J.K. Treatable traits and therapeutic targets: Goals for systems biology in infectious disease. *Current Opinion in Systems Biology* **2**, 139–145(2017).

15.Baillie, J.K., Bretherick, A., Haley, C.S., Clohisey, S., Gray, A., Neyton, L.P.A., Barrett, J., Stahl, E.A., Tenesa, A., Andersson, R., Brown, J.B., Faulkner, G.J., Lizio, M., Schaefer, U., Daub, C., Itoh, M., Kondo, N., Lassmann, T., Kawai, J., Mole, D., Bajic, V.B., Heutink, P., Rehli, M., Kawaji, H., Sandelin, A., Suzuki, H., Satsangi, J., Wells, C.A., Hacohen, N., Freeman, T.C., Hayashizaki, Y., Carninci, P., Forrest, A.R.R. & Hume, D.A. Shared activity patterns arising at genetic susceptibility loci reveal underlying genomic and cellular architecture of human disease. *PLoS computational biology* **14**, e1005934(2018).

16.Baillie, J.K. Targeting the host immune response to fight infection. *Science* **344**, 807–808(2014).