Evidenz vs. Eminenz

Christopher Rugg
Klinik für Anästhesie und Intensivmedizin
Innsbruck

Zwischen Wissenschaft und Weisheit – ein Machtkampf in der Medizin

1793
„An attempt to improve the Evidence of Medicine“
George Fordyce,
Schottland

1993
Gründung der Chochrane Collaboration, London, UK

2024
> 12.000 Reviews durch Cochrane publiziert
>1200 University of Oxford;
>25% aus den UK

1972
„Effectiveness and Efficiency: Random Reflections on Health Services “
Archie Cochrane, UK

1998
Gründung “Netzwerk Evidenzbasierte Medizin“ im deutschsprachigen Raum

Evidenzgrade

Evidenzgrad	Beschreibung
Ia	Metaanalyse von randomisierten kontrollierten Studien (RCTs)
Ib	Mindestens eine gut durchgeführte RCT
IIa	Gut durchgeführte kontrollierte Studie ohne Randomisierung
IIb	Quasi-experimentelle Studie (z. B. Vergleich mit historischen Kontrollen)
III	Nicht-experimentelle Studien, z. B. Fall-Kontroll- oder Kohortenstudien
IV	Meinungen von angesehenen Experten, Konsensuspapiere, Fallberichte

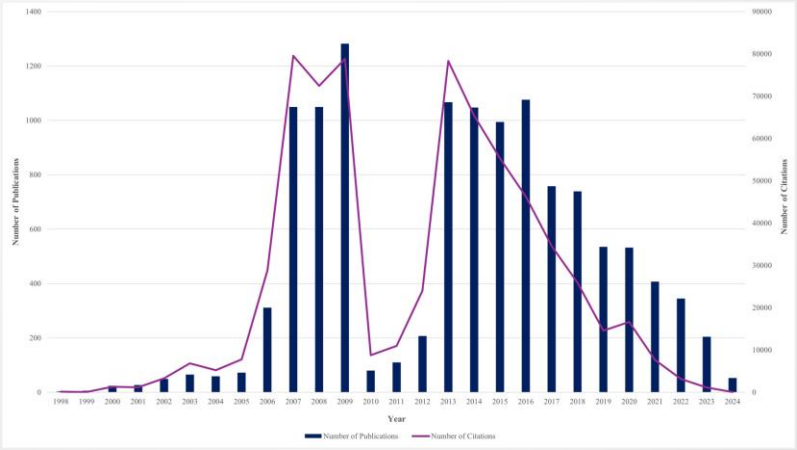
Evidenzqualität

Evidenzqualität	Bedeutung
⨁⨁⨁⨁ Hoch	Weitere Forschung ist sehr unwahrscheinlich, das Vertrauen in den Effekt ist hoch.
⨁⨁⨁◯ Mittel	Weitere Forschung kann den Effekt verändern; Vertrauen ist mäßig.
⨁⨁◯◯ Niedrig	Weitere Forschung wird den Effekt wahrscheinlich verändern.
⨁◯◯◯ Sehr niedrig	Die Schätzung des Effekts ist sehr unsicher.

Empfehlungsstärke

Empfehlungsstärke	Bedeutung
↑↑ Stark (Strong)	„Wir empfehlen…" – Gilt für die meisten Patienten, sollte standardmäßig erfolgen.
⚖ Schwach (Conditional)	„Wir schlagen vor…" – Abhängig von Situation, Präferenzen und Kontext.

Publikationen durch Cochrane



Sharifan A., Analysis of Cochrane systematic reviews: A comprehensive study of impact and influence from 1998 to 2024, Cochrane Evidence Synthesis and Methods, 2024

Kritikpunkte EbM

- Medizinische Statistik: 5% Fehlerwahrscheinlichkeit. 80% power.
- Zu enge Auslegung. „Evidence" ist nicht immer fehlerfrei generierbar.
  - Absence of evidence is not evidence of absence
  - Sachverhalte, die seit langem und vollkommen geklärt sind, für die aber im Sinne der EbM keine ausreichenden Nachweise vorliegen – RCT ethisch nicht vertretbar
  - Bias durch Firmensponsoring (finanzielle und strukturelle Hürden von RCTs)
  - Publikationsbias – negative Studien werden oft nicht veröffentlicht > Einfluss auf Metaanalysen
  - Durchführungsbias – Schlagwort Pädiatrie, RCTs extrem erschwert durchführbar -> häufig Vereinfachung des Studiendesigns („alle über einen Kamm scheren")
  - Problem der Heterogenität der Untersuchungsgegenstände
  - Probleme in der Fragestellung/Methodik/Auswahl der Outcome-Parameter (Fokus auf Mortalität)
  - …

Wenn Daten und Deutung aufeinanderprallen

Sepsis guidelines 2016 - Antithrombin

1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).

Rationale. Antithrombin is the most abundant anticoagulant circulating in plasma. The decrease of its plasma activity at onset of sepsis correlates with disseminated intravascular coagulation (DIC) and lethal outcome. However, a phase III clinical trial of high-dose antithrombin for adults with sepsis and septic shock as well as systematic reviews of antithrombin for critically ill patients did not demonstrate any beneficial effect on overall mortality. Antithrombin was associated with an increased risk of bleeding (340, 341). Although post hoc subgroup analyses of patients with sepsis associated with DIC showed better survival in patients receiving antithrombin, this agent cannot be recommended until further clinical trials are performed.

Rhodes A., et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine

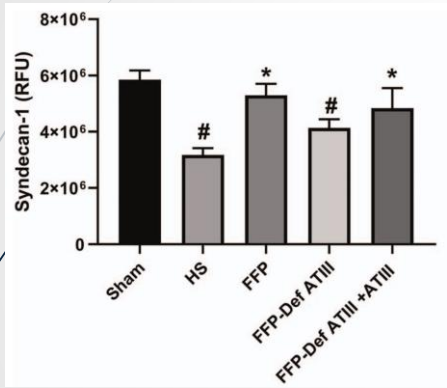
Review > Cochrane Database Syst Rev. 2016 Feb 8;2(2):CD005370.
doi: 10.1002/14651858.CD005370.pub3.

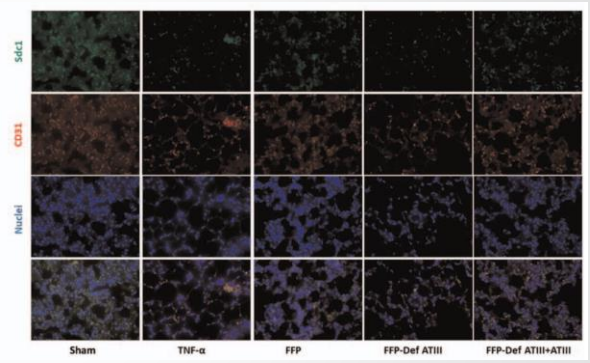
Antithrombin III for critically ill patients

Mikkel Allingstrup [1], Jørn Wetterslev, Frederikke B Ravn, Ann Merete Møller, Arash Afshari

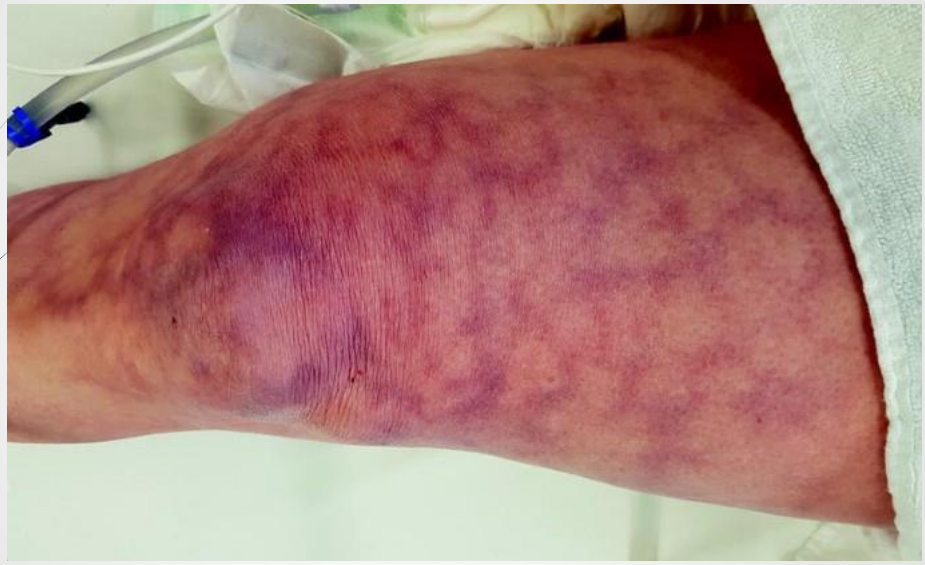
Authors' conclusions: There is insufficient evidence to support AT III substitution in any category of critically ill participants including the subset of patients with sepsis and DIC. We did not find a statistically significant effect of AT III on mortality, but AT III increased the risk of bleeding events. Subgroup analyses performed according to duration of intervention, length of follow-up, different patient groups, and use of adjuvant heparin did not show differences in the estimates of intervention effects. The majority of included trials were at high risk of bias (GRADE; very low quality of evidence for most of the analyses). Hence a large RCT of AT III is needed, without adjuvant heparin among critically ill patients such as those with severe sepsis and DIC, with prespecified inclusion criteria and good bias protection.

Antithrombin III und die Glykokalyx





Lopez E. et al. Antithrombin III Contributes to the Protective Effects of Fresh Frozen Plasma Following Hemorrhagic Shock by Preventing Syndecan-1 Shedding and Endothelial Barrier Disruption. SHOCK 53(2):p 156-163, February 2020.



Reitgruber, D., Auer, J. (2021). Hämodynamik und Kreislaufunterstützung. In: Internistische Intensivmedizin für Einsteiger. Springer, Berlin, Heidelberg.

Sepsis guidelines 2021

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
HEMODYNAMIC MANAGEMENT		
32. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.	***Strong,*** *moderate-quality evidence*	
33. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.	***Weak,*** *low quality of evidence*	**CHANGED from *weak recommendation*,** *low quality of evidence.* "We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"

Evans L, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Table 2. Clinical Outcomes.*

Outcome	Balanced Crystalloids (N=7942)	Saline (N=7860)	Adjusted Odds Ratio (95% CI)†	P Value†
Primary outcome				
Major adverse kidney event within 30 days — no. (%)‡	1139 (14.3)	1211 (15.4)	0.90 (0.82 to 0.99)	0.04
Components of primary outcome				
In-hospital death before 30 days — no. (%)	818 (10.3)	875 (11.1)	0.90 (0.80 to 1.01)	0.06
Receipt of new renal-replacement therapy — no./total no. (%)§	189/7558 (2.5)	220/7458 (2.9)	0.84 (0.68 to 1.02)	0.08
Among survivors	106/6787 (1.6)	117/6657 (1.8)		
Final creatinine level ≥200% of baseline — no./total no. (%)§	487/7558 (6.4)	494/7458 (6.6)	0.96 (0.84 to 1.11)	0.60
Among survivors	259/6787 (3.8)	273/6657 (4.1)		
Among survivors without new renal-replacement therapy	215/6681 (3.2)	219/6540 (3.3)		

Semler MW et al. SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018

Fluid Type	Volume			Sodium	Chloride
	%	Mean daily fluid volume in mL ± SD	Median daily fluid volume in mL (IQR)	Mean daily amount in mmol ± SD	Mean daily amount in mmol ± SD
Resuscitation fluids	6.5%	151 ± 439	0 (0-100)	21 ± 63	17 ± 49
Isotonic crystalloids (rate >1L/6h)	1.6%	36 ± 256	0 (0-0)	5 ± 36	4 ± 28
Colloids (mainly albumin and gelatins)	4.9%	114 ± 331	0 (0-98)	16 ± 48	13 ± 37
Blood products	3.2%	75 ± 318	0 (0-0)	11 ± 48	7 ± 29
Maintenance and replacement fluids	24.7%	574 ± 606	334 (150-894)	68 ± 78	79 ± 78
Glucose-containing crystalloids	22.3%	517 ± 506	296 (150-812)	59 ± 65	73 ± 70
Isotonic crystalloids (rate ≤1L/6h)	2.5%	57 ± 273	0 (0-0)	8 ± 39	6 ± 31
Nutrition	33.0%	766 ± 688	630 (0-1401)		
Enteral nutrition	19.0%	441 ± 593	0 (0-995)	20 ± 28	15 ± 21
Parenteral nutrition	7.8%	182 ± 492	0 (0-0)	0 ± 0[a]	0 ± 0[a]
Oral fluid intake	6.2%	143 ± 319	0 (0-150)	N/A	N/A
Fluid creep	32.6%	757 ± 608	645 (308-1039)		
Volume due to concentrated electrolytes	2.4%	56 ± 62	42 (22-72)	9 ± 50	10 ± 33
Volume used to keep venous access open	0.8%	20 ± 43	0 (0-28)	3 ± 7	3 ± 8
Intermittent and continuous medication	29.3%	681 ± 580	565 (251-946)	N/A	N/A
Total amount	100%	2,322 ± 1,315	2,296 (1,422-3,069)	131 ± 137	130 ± 111

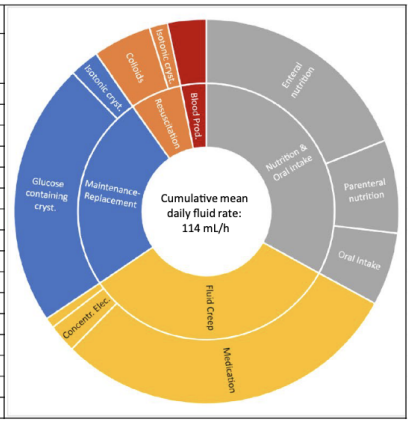
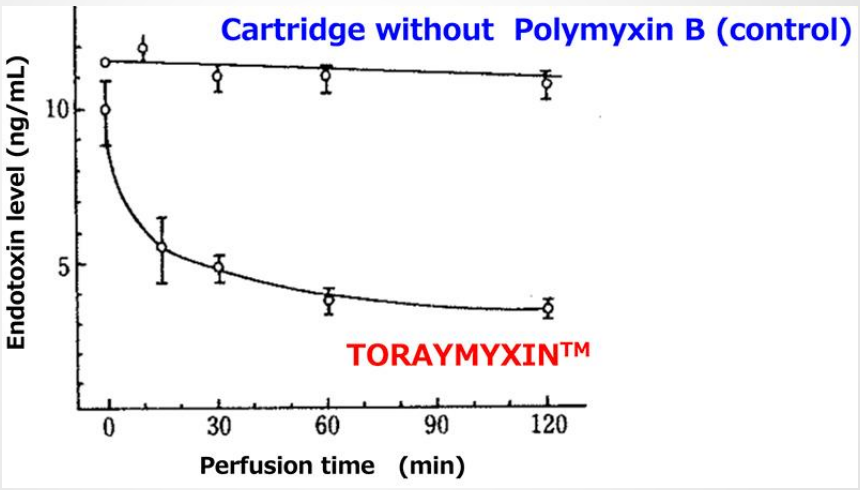


Fig. 1 Proportion, mean, and median fluid volumes, and mean sodium and chloride burdens of the different fluid types (average of 14,654 patients on their cumulative 103,098 days of ICU stay), including a graphic representation of the distribution of the different mean daily fluid volumes. Mean duration of one ICU day, 20.3 ± 6.7 h. SD standard deviation, IQR interquartile range, N/A data not available. [a]To ensure optimal electrolyte management in our ICU, only electrolyte-free formulas of parenteral nutrition are prescribed, with separate administration of electrolytes

Regenmortel N., et al.. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Medicine 44, 409–417 (2018).

Sepsis und Hämoadsorption

Sepsis und Polymyxin B



Sepsis und Polymyxin B

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
59. For adults with sepsis or septic shock we suggest against using polymyxin B hemoperfusion.	***Weak,*** *low quality of evidence*	**NEW from previous:** "We make no recommendation regarding the use of blood purification techniques"

Evans L, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021

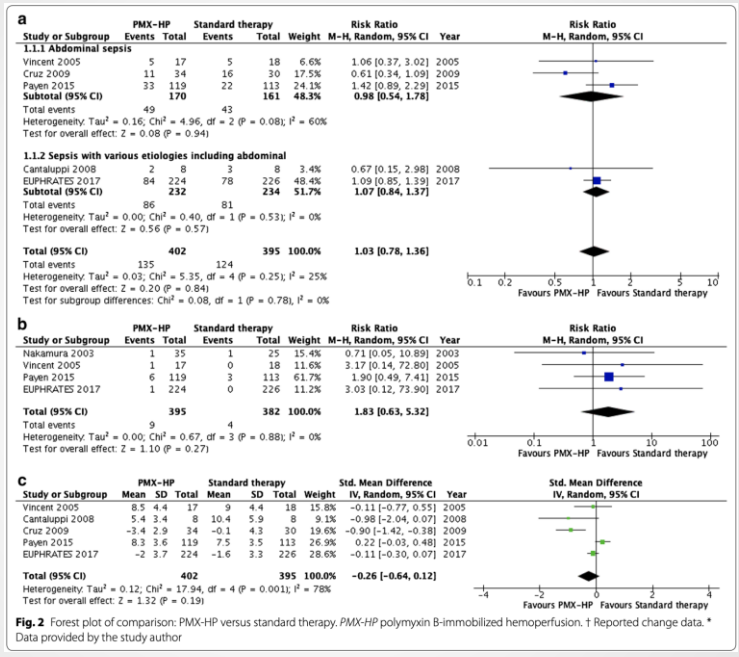


Fig. 2 Forest plot of comparison: PMX-HP versus standard therapy. *PMX-HP* polymyxin B-immobilized hemoperfusion. † Reported change data. * Data provided by the study author

Fujii, T, et al. Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 44, 167–178 (2018)

ORIGINAL

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

Methods: Post-hoc analysis of the EUPHRATES trial for the 194 patients with EAA ≥ 0.6–0.89 who completed two treatments (PMX or sham). The primary end point was mortality at 28 days adjusted for APACHE II score and baseline mean arterial pressure (MAP). Additional end points included changes in MAP, cumulative vasopressor index (CVI), median EAA reduction, ventilator-free days (VFD), dialysis-free days (DFD) and hospital length of stay. Subpopulations analyzed were site and type of infection and those with norepinephrine dose > 0.1 mcg/kg/min at baseline.

Klein DJ, et al. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018

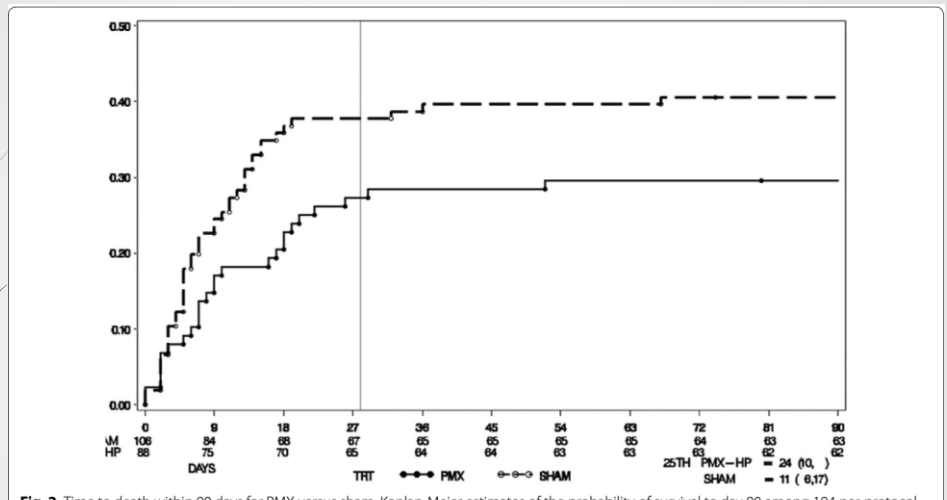


Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE II score are the hazard ratio [0.57, 95% CI (0.35, 0.93), *P* value = 0.02]. The vertical line represents the 28-day interval. The 28-day adjusted Cox proportional hazard ratio for death in the PMX group compared with the sham group is 0.58 (95% CI, 0.35 to 0.98; *P* = 0.04). *TRT* treatment, *25th* 25th percentile at 90 days

Klein DJ, et al. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med. 2018

ARDS und Glukokortikoide

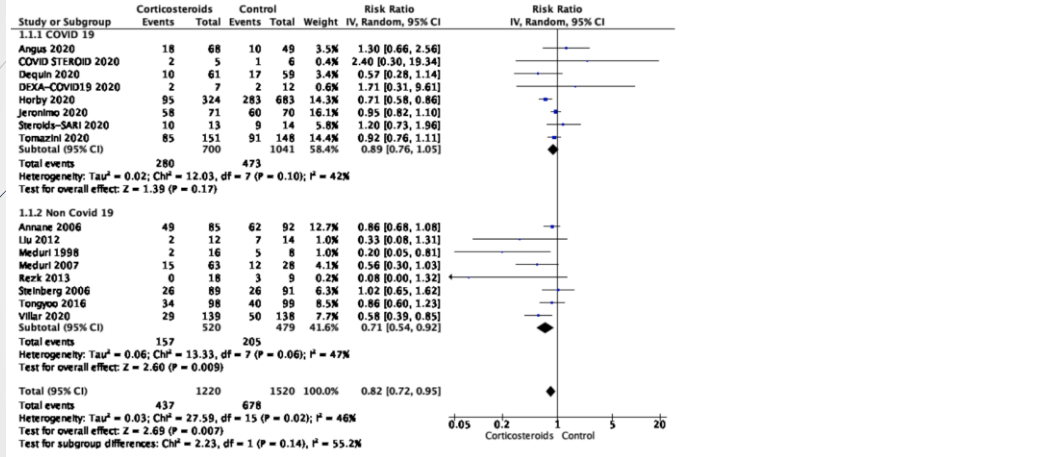
2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

Chaudhuri, Dipayan MD, MSc, FRCPC[1,2]; Nei, Andrea M. PharmD, FCCM[3]; Rochwerg, Bram MD, MSc, FRCPC, FCCM[1,2]; Balk, Robert A. MD, MCCM[4]; Asehnoune, Karim MD[5]; Cadena, Rhonda MD, FNCS, FCCM[6]; Carcillo, Joseph A. MD[7]; Correa, Ricardo MD[8]; Drover, Katherine BHSc[9]; Esper, Annette M. MD, MSc[10]; Gershengorn, Hayley B. MD, ATSF, FCCM[11,12]; Hammond, Naomi E. RN, BN, MN, MPH[13,14]; Jayaprakash, Namita MB, MD, BcH, BAO[15,16]; Menon, Kusum MD, MSc[17,18]; Nazer, Lama PharmD, FCCM[19]; Pitre, Tyler MD[1,2]; Qasim, Zaffer A. MD[20]; Russell, James A. MD[21]; Santos, Ariel P. MD, MPH, FCCM[22]; Sarwal, Aarti MD, FCCM, FAAN, FNCS[23]; Spencer-Segal, Joanna MD, PhD[24]; Tilouche, Nejla MD[25]; Annane, Djillali MD, PhD (Chair)[26,27,28]; Pastores, Stephen M. MD, MACP, FCCP, FCCM (Chair)[29]

ARDS und Glukokortikoide

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Acute respiratory distress syndrome		
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence	We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (Pao_2/Fio_2 of < 200 and within 14 d of onset) (conditional recommendation, moderate quality of evidence)

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with ARDS. Grouped by COVID-19 Status. 28 day Mortality.
Df = degrees of freedom



Chaudhuri, et al. 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia. Critical Care Medicine 52(5):p e219-e233, May 2024.

ARDS und Glukokortikoide

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

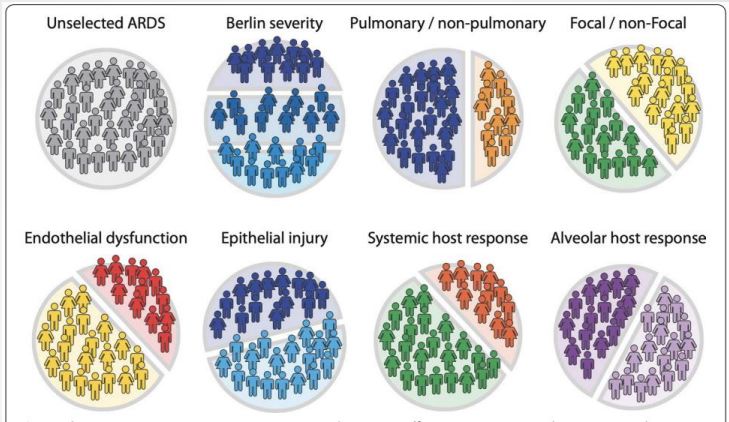


Fig. 1 There are many ways to parse ARDS into subgroups. Different ways to parse the ARDS population into subgroups some of which are subphenotypes. One patient can, therefore, belong to many different subgroups simultaneously, each of which could be a treatable trait. Top row from left to right: unselected ARDS; Berlin severity with mild, moderate and severe ARDS based on PaO2/FiO2 (light to dark blue); pulmonary (dark blue) and non-pulmonary (light orange) causes for ARDS; Focal (green) and non-Focal (yellow) ARDS based on chest CT. Bottom row from left to right: patients with (red) and without (yellow) apparent endothelial dysfunction; with (dark blue) and without (light blue) apparent epithelial injury; hyperinflammatory (orange) and hypoinflammatory systemic host response; hyperinflammatory (dark purple) and hypoinflammatory (light purple) alveolar host response

Bos, L.D.J., Laffey, J.G., Ware, L.B. et al. Towards a biological definition of ARDS: are treatable traits the solution?. ICMx 10, 8 (2022)

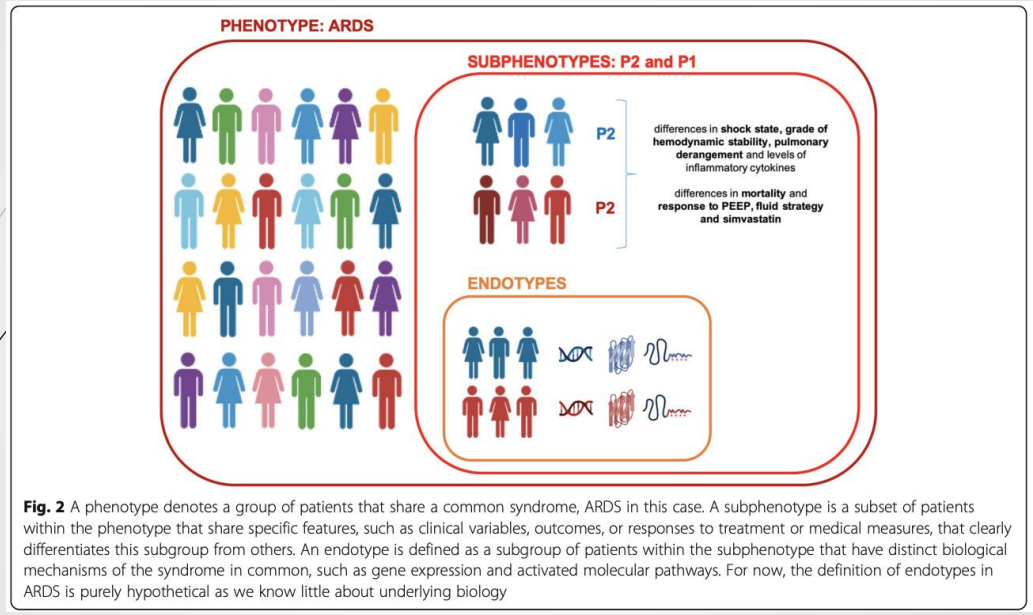


Fig. 2 A phenotype denotes a group of patients that share a common syndrome, ARDS in this case. A subphenotype is a subset of patients within the phenotype that share specific features, such as clinical variables, outcomes, or responses to treatment or medical measures, that clearly differentiates this subgroup from others. An endotype is defined as a subgroup of patients within the subphenotype that have distinct biological mechanisms of the syndrome in common, such as gene expression and activated molecular pathways. For now, the definition of endotypes in ARDS is purely hypothetical as we know little about underlying biology

Wildi, K., Livingstone, S., Palmieri, C. et al. The discovery of biological subphenotypes in ARDS: a novel approach to targeted medicine?. j intensive care 9, 14 (2021).

EbM der Zukunft

EbM derzeit

Standard medicine
(one size fits all)

- *Low Tidal Volume*
- *PEEP-FiO$_2$ Table*

Personalized medicine

- *Individualized Tidal Volume*
- *Individualized PEEP*
  - Esophageal balloon manometry
  - Recruitment/Inflation Index
  - Electrical Impedance Tomography
- *ARDS Phenotyping*
  - Inflammatory sub phenotypes

Hoshino T, Yoshida T. Future directions of lung-protective ventilation strategies in acute respiratory distress syndrome. Acute Med Surg. 2024

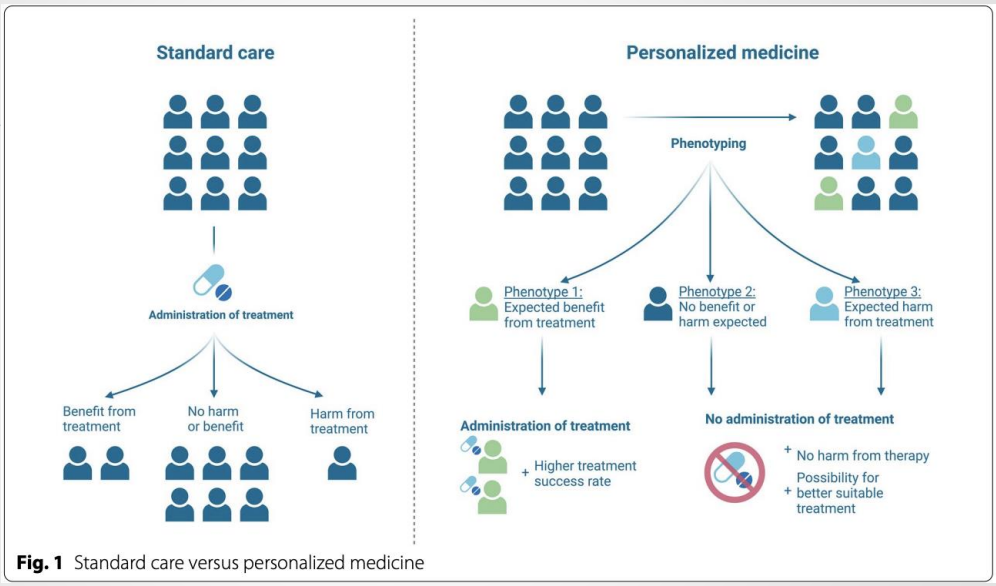


Fig. 1 Standard care versus personalized medicine

Bakkerus, L., Pickkers, P. Personalized medicine in COVID-19. Intensive Care Med 48, 1607–1610 (2022)

Zusammenfassung

- Heißt EbM nur tun was gesichert hilft?
  - Evidenzgenerierende Studien leiden durchaus an Bias:
    - Heterogenität der Untersuchungsgruppe
      - Interventionen die in dieser Masse einen kleinen Effekt gebracht haben, können manchen viel Nutzen bringen, aber manchen durchaus Schaden
      - Interventionen die in dieser Masse keinen (oder gar negativen) Effekt haben, können manchen durchaus viel Nutzen bringen
    - Methodische Probleme
      - Effekt wird nicht gesehen weil Confounder übersehen werden
    - Wahl der Outcome Parameter
      - Immer nur Mortalität?
    - Erschwerte Durchführung / Sponsoring-bias / Publikations-bias
  - Auf Ebene des Individuums ist eine personalisierte Medizin derzeit oft eminenzbasiert

Zusammenfassung

- Ziel derzeit:
  - Jenseits von Leitlinien mithilfe der vorhandenen Evidenz das beste für den Patienten als Individuum erreichen
  - Auch die Rationale der Leitlinien verstehen und hinterfragen
    - keine „Evidenz“ weil eh klar
    - Empfehlung trotz Heterogenität der Patienten
    - Keine Empfehlung weil keine klare Evidenz aufgrund einer heterogenen Gruppe
    - Keine Empfehlung weil keine klare Evidenz und “Standard of care“ günstiger?
    - Viele Interventionen verteufelt weil Heterogenität den Effekt auf Subgruppe verschleiert (Polymyxcin B, aktiviertes Protein C, Antithrombin III)

Gemeinsam heilen: Wenn Erfahrung auf Evidenz trifft

„Die Evidenzbasierte Medizin (EbM) hat zum Ziel, dass Behandlungsentscheidungen für den einzelnen Patienten auf der Basis der individuellen Erfahrung des Arztes unter Berücksichtigung der besten verfügbaren Evidenz in Abwägung der Wünsche und Vorstellungen des Patienten getroffen werden.“

Schmucker et al.: Manual der »Cochrane Collaboration« für die Leitlinienerstellung zur Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien 2016