

Relevanz klinischer Endpunkte in der Intensivmedizin: Methodische Analyse anhand
systematischer Übersichtsarbeiten

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Auflistung der Publikationen

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Weitere Publikationen/Veröffentlichungen

- Steinfeld, E., **Dahms, K.**, Dormann, J., Ansems, K., Janka, H., Metzendorf, M.-I., Marx, G. Benstoem, C., Breuer, T. (2025). Examining the Impact of Validated Handover Protocols on Treatment Outcomes in Polytrauma Patients: A Systematic Review. European Journal of Trauma Emergency Surgery, 51.
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REVIEW

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Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis

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Abstract

Background At the end of 2021, the European Medicines Agency (EMA) expanded its approval for the recombinant human interleukin-1 (IL-1) receptor antagonist Anakinra for the treatment of COVID-19 patients with elevated soluble urokinase plasminogen activator receptor (suPAR). However, the role of Anakinra in COVID-19 remains unanswered, especially in patients receiving different forms of respiratory support. Therefore, the objective of this systematic review is to assess the safety and effects of Anakinra compared to placebo or standard care alone on clinical outcomes in adult hospitalized patients with SARS-CoV-2 infection.

Methods We searched the Cochrane COVID-19 Study Register (comprising MEDLINE, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, medRxiv, and the Cochrane Central Register of Controlled Trials (CCSR)) and the WHO COVID-19 Global literature on coronavirus disease database to identify completed and ongoing studies from inception of each database to December 13, 2021. Since then, we monitored new published studies weekly up to June 30, 2022 using the CCSR. We included RCTs comparing treatment with Anakinra to placebo or standard care alone in adult hospitalized patients with SARS-CoV-2 infection.

Results We included five RCTs with 1,627 patients ($n_{\text{Anakinra}} = 888$, $n_{\text{control}} = 739$, mean age 59.63 years, 64% male). Random-effects meta-analysis was used to pool data. We found that Anakinra makes little or no difference to all-cause mortality at up to day 28 compared to placebo or standard care alone (RR 0.96, 95% CI 0.64–1.45; RD 9 fewer per 1000, 95% CI 84 fewer to 104 more; 4 studies, 1593 participants; $I^2 = 49\%$; low certainty of evidence).

Conclusions Anakinra has no effect on adult hospitalized patients with SARS-CoV-2 infection regarding mortality, clinical improvement and worsening as well as on safety outcomes compared to placebo or standard care alone.

Trial Registration: PROSPERO Registration Number: CRD42021257552.

Keywords Anakinra, Interleukin 1 receptor antagonist protein, SARS-CoV-2, Hospitalization, Meta-analysis, Systematic review, COVID-19

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Background

Despite intensive international efforts to contain its spread and unprecedented record-speed vaccine roll-out and distribution, SARS-CoV-2 has resulted in a continuously rising number of confirmed cases and deaths [1, 2], causing severe impact on healthcare facilities, healthcare workers and medical equipment.

Currently, effective treatment options are still sparse [3]. For prophylaxis and treatment, excessive immunological processes play a crucial role. Until today, there is a need for an effective anti-inflammatory and immunomodulatory therapy in COVID-19 patients. As the evidence on many of the substances that were investigated during the pandemic increased, national and international guidelines emerged to support daily clinical decisions [4–6]. However, only a few substances with proven benefits for the treatment of COVID-19 exist, such as systemic corticosteroids, interleukin-6 receptor antagonists or Janus kinase inhibitors [3].

At the end of December 2021, the European Medicines Agency (EMA) expanded its approval for the recombinant human interleukin-1 (IL-1) receptor antagonist Anakinra (r-metHuIL-1ra). Anakinra received approval for the treatment of COVID-19 patients with elevated soluble urokinase plasminogen activator receptor (suPAR). Anakinra was already approved for the treatment of certain rheumatologic diseases, i.e., rheumatoid arthritis (RA) and Still's Disease [7]. IL-1 is a pro-inflammatory cytokine that is dysregulated in patients with severe SARS-CoV-2 infection and associated with clinical progression in COVID-19 [8]. In addition, epithelial damage by SARS-CoV-2 with a release of IL-1 β is discussed, which leads to the release of more IL-1 to recruit and activate additional innate immune cells. By competitively inhibiting the binding of cytokines to interleukin receptor antagonists, Anakinra has the potential to control active inflammation and can potentially interrupt the autoinflammatory loop [9]. Despite the approval for patients with elevated suPAR, based on data from one randomized clinical trial [10], the role and therapeutic potential of IL-1 inhibition in COVID-19 remains unanswered, especially in patients receiving different forms of respiratory support, in combination or even in comparison with other immunomodulatory substances.

The objective of this systematic review and meta-analysis is to assess the safety and effects of Anakinra compared to placebo or standard care alone on clinical outcomes in adult hospitalized patients with SARS-CoV-2 infection.

Methods

Differences to protocol are described in the Additional file 1. The protocol for this review was registered with PROSPERO on May 28, 2021 (CRD42021257552).

Eligibility criteria

We included randomized controlled trials (RCTs) reported as full texts, abstract only and unpublished data. We included studies comparing treatment with Anakinra to placebo or standard care alone in adult hospitalized patients with SARS-CoV-2 infection.

Systematic search

Our Information Specialist (M.I.M.) conducted a systematic search in the following sources from inception of each database to December 13, 2021 with no restrictions on the language of publication:

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
 - MEDLINE (PubMed), daily updates;
 - Embase, weekly updates;
 - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
 - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates;
 - medRxiv (www.medrxiv.org), weekly updates;
 - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.
- WHO COVID-19 Global literature on coronavirus disease (<https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/>), comprising over 15 primary sources.

Details of our search strategy are provided in the Additional file 2. Since the date of last search, we monitored new published studies weekly up to June 30, 2022 using the CCSR. Moreover, we identified other potentially eligible studies by searching the reference lists of included studies, systematic reviews and meta-analyses. We contacted authors for missing data.

Selection of studies

We imported citations from the systematic search into Rayyan [11]. Two authors independently screened the titles and abstracts of all potential studies (K.D., K.A.). Full-text study publications were retrieved, imported into Excel and screened by two authors independently (K.D.,

K.A.). Reasons for exclusion of ineligible studies were recorded (Additional file 3). Any disagreements were resolved through discussion or, if required, consultation with a third author (A.M., C.B., M.S.).

Data extraction process

We used a customised data collection form developed in Microsoft Excel [12] to collect study data (extraction tables can be requested via E-Mail). As primary outcome, we assessed all-cause mortality (day 28, day 60, time-to-event, and up to longest follow-up) and as secondary outcomes clinical status, quality of life, serious adverse events (SAE) and adverse events (AE). Extraction of study characteristics and outcome data of included studies was conducted by one author and checked by another (K.D., A.M., K.A.). Any disagreements were resolved by discussion or by consulting a third review author if necessary. Two authors transmitted the outcome data into the Cochrane statistical software RevMan 5.3 [13], which was checked by a third author (A.M.).

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias of included studies (K.D., K.A.) using the RoB 2 tool (beta version 7) [14]. RoB 2 addresses five domains of bias (randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results). The signalling questions recommended in the tool were used to make a judgement according to the available options. Algorithms proposed in RoB 2 were used to assign each domain and the overall risk of bias, a level of bias (low risk of bias, some concerns, high risk of bias). We resolved any disagreements by discussion or by involvement of another author (A.M., M.S., C.B.).

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both groups. We performed analyses using the mean difference (MD) with 95% confidence intervals (CI), if outcomes used the same scale. For dichotomous outcomes, analysed as risk ratios (RR) with 95% CI, we recorded the number of events and the total number of participants in both intervention groups. If sufficient information was available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes. We contacted authors to obtain missing numerical outcome data when possible.

Assessment of heterogeneity

We assessed statistical heterogeneity by the visual inspection of forest plots within the Review Manager (RevMan 5) software [13] and using the χ^2 test with a

significance level of $P < 0.1$. We assessed statistical heterogeneity in each meta-analysis using I^2 statistics ($I^2 > 30\%$ to signify moderate heterogeneity, $I^2 > 75\%$ to signify considerable heterogeneity) [15]. If I^2 was above 75% or if there was inconsistency among the trials in the direction or magnitude of effects (judged visually), we explored possible causes for heterogeneity and used sensitivity analysis rather than subgroup analysis. Meta-analysis was not performed if no reasons for heterogeneity could be identified. Instead, the results were presented in tables.

Assessment of reporting biases

We searched trial registries to identify completed trials that were not published elsewhere, to minimise or determine publication bias. As no more than 10 trials were included in our meta-analyses, we did not create a funnel-plot to explore potential publication bias.

Data synthesis

We performed meta-analyses only, if the clinical and methodological characteristics of individual studies were sufficiently homogeneous. Placebo and standard care were treated as the same intervention. We used RevMan 5.3 for all analyses [13]. Data entry into the RevMan software was checked by a second review author for accuracy (A.M., K.D., K.A.). As we anticipated that true effects would be related, but not the same for the studies included in our review, we performed random-effects meta-analyses. For continuous outcomes, we calculated mean differences with 95% CIs. We performed analyses using the inverse variance method under a random-effects model. For binary outcomes, we performed analyses using the Mantel–Haenszel method under a random-effects model to report pooled risk ratios with 95% CI.

Summary of findings and assessment of the certainty of the evidence

We used MAGICapp software [16] to create a summary of findings table and evaluated the certainty of the evidence (A.M., C.B., M.S., K.A., K.D.) using the GRADE approach for interventions evaluated in RCTs.

Results

Study selection

The search identified 240 records. After removing duplicates, we screened 205 records based on title and abstract, of which 167 studies did not meet the prespecified inclusion criteria and were excluded. We screened the full texts and trial register entries of the remaining 38 references. Since the date of the last search, we monitored new published studies weekly until April 29, 2022 using CCSR. No additional full texts were identified.

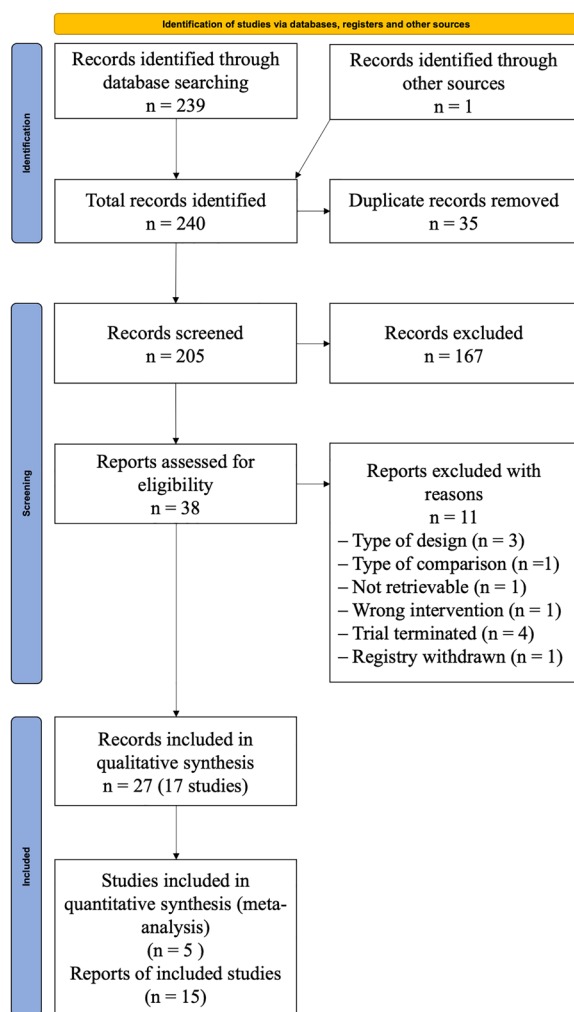


Fig. 1 Flowchart of the systematic review selection process

Eleven records were excluded for different reasons (Fig. 1, Additional file 3) [17–27]. The remaining 27 records were included for qualitative synthesis [10, 28–53]. Five RCTs were included in our meta-analysis: Declercq et al. [28–30], Derde et al. [31–34], Kharazmi et al. [35], Kyriazopoulou et al. [10, 36–39] and Tharaux et al. [40].

Study characteristics

Five RCTs [10, 28, 31, 35, 40], of which one is a pre-print, with a total of 1,627 adult participants (mean age 59.63 years, 64% male) diagnosed with SARS-CoV-2 infection met the criteria for inclusion and were analysed in our meta-analysis. All included RCTs used a parallel-group design. One study included only patients with elevated suPAR levels [10]. There was variability regarding setting, Anakinra dosage and duration as well as concomitant medication (Table 1). Additional study characteristics are provided in the Additional file 4.

Between November 26, 2021 and February 17, 2022, we contacted the five corresponding authors to obtain missing data. Eventually, one author provided additional study characteristics and outcome data [28].

Risk of bias assessment

The overall risk of bias among the five RCTs was low or some concerns for most outcomes due to lack of blinding among clinicians and outcome assessors as well as baseline differences (Additional file 5).

Effects of interventions

Anakinra compared to placebo or standard care alone (Table 2).

All-cause mortality

Four studies reported all-cause mortality at up to day 28 for 1593 participants (Fig. 2). We found that Anakinra makes little or no difference to all-cause mortality at up to day 28 compared to placebo or standard care alone (RR 0.96, 95% CI 0.64–1.45; risk difference (RD) 9 fewer per 1000, 95% CI 84 fewer to 104 more; 4 studies, 1593 participants; $I^2=49\%$; low certainty of evidence). The reason for downgrading was serious inconsistency due to inconsistent direction and widely varying point estimates and serious imprecision due to wide CIs and that the CI includes both benefits and harms.

Analyses regarding all-cause mortality at up to 60 days, time-to-event and at hospital discharge are reported in the supplements (Additional file 6: Figs. S1–S4).

Worsening of clinical status

New need for invasive mechanical ventilation or death

Two studies reported this outcome at day 28 for 709 participants (Fig. 3). We found that treatment with Anakinra has no effect on the risk for invasive mechanical ventilation (RR 0.69, 95% CI 0.31–1.56; RD 43 fewer per 1000, 95% CI 95 fewer to 77 more; 2 studies, 709 participants; $I^2=65\%$; low certainty of evidence). Our main reason for downgrading was serious inconsistency due to statistical heterogeneity, inconsistent direction and widely varying point estimates and serious imprecision due to wide CIs and that the CI includes both benefits and harms.

One study reported this outcome at day 28 in 594 patients with increased suPAR levels (Fig. 3, Kyriazopoulou and Additional file 6: Fig. S5). We found that treatment with Anakinra probably decreases the risk for a new need for invasive mechanical ventilation or death (RR 0.49, 95% CI 0.29–0.83; RD 65 fewer per 1000, 95% CI 90 fewer to 22 more; 1 study, 594 participants; I^2 not applicable; moderate certainty of evidence). Our main

Table 1 Characteristics of included studies

References	Setting; Study-design	Participants allocated, n	Age, years	Severity of condition according to respiratory support (n/N (%))	Anakinra (A) dosage	Control (C)	Concomitant medication
Declercq et al. [28]	Inpatient Multicenter in Belgium; randomized, controlled, open-label	N ^{total} : 118 (with other interventions: 342) n ^{Anakinra} : 43 ^a n ^{Control} : 72	Median (IQR): A: 65 (54–70) C: 63 (56–73)	IMV: A: 8/43 (19); C: 9/72 (13) non-IMV: A: 16/43 (37); C: 23/72 (32) supplemental oxygen only ^b : A: 19/43 (44); C: 39/72 (54) Not requiring supplemental oxygen: A: 0/43 (0); C: 1/72 (1)	100 mg (s.c.) daily for 28 days or until hospital discharge on top of standard of care If glomerular filtration rate < 30 ml/min per 1.73 m ² , the dosing was lowered to 100 mg once every other day	Standard of Care (not specified)	Antibiotics A: 21 (49%); C: 34 (47%) Glucocorticoids A: 29 (67%); C: 43 (60%) Hydroxychloroquine A: 7 (16%); C: 8 (11%) Remdesivir A: 3 (7%); C: 3 (4%)
Derde et al. [31]	Inpatient Multicenter in UK, Australia, Netherlands, Ireland, New-Zealand, Canada, Finland, Italy and Saudi Arabia; randomized, controlled, open-label	N ^{total} : 771 (with other interventions: 2216) n ^{Anakinra} : 373 n ^{Control} : 406	Mean (SD): Severe State A: 59.8 (11.9) C: 61.1 (12.9) Moderate State A: 36.0 (17.0) C: 67.0 (13.7)	IMV: A: 138/373 (37); C: 122/406 (30) ECMO: A: 0/373 (0); C: 1/406 (0) No respiratory support/supplemental oxygen only: A: 1/373 (0); C: 2/406 (0)	300 mg (i.v.) as loading dose, followed by 100 mg every 6 h on days 1–14 or until either free from IMV for more than 24 h, or discharge from ICU If creatinine clearance < 30 ml/min or receiving renal replacement therapy, the dosing interval was increased to 12 h	Standard of Care (not specified)	Remdesivir (n (%)) A: 109 (29.5); C: 105 (26.1) Steroids (n (%)) A: 317 (85.9); C: 269 (66.9%)
Kharazmi et al. [35]	Inpatient One center in Iran; randomized, controlled, open-label	N ^{total} : 30 n ^{Anakinra} : 15 n ^{Control} : 15	Mean (SD): A: 49.25 (19.12) C: 59.00 (1.79)	IMV or ECMO: A: 2/15 (13); C: 3/15 (20) non-IMV or high flow oxygen: A: 10/15 (67); C: 6/15 (40) low flow supplemental oxygen only: A: 3/15 (20); C: 6/15 (40)	100 mg (i.v.) daily until discharge or a maximum of 14 days	Standard of Care (not specified)	Corticosteroid A: 11 (73.3%); C: 8 (53.3%) Favipiravir A: 9 (60%); C: 4 (26.67%) Interferon A: 14 (93.3%); C: 9 (60%) Lopinavir/ritonavir A: 7 (46.67%); C: 12 (80%) Remdesivir A: 2 (13.33%); C: 4 (26.67%)

Table 1 (continued)

References	Setting; Study-design	Participants allocated, n	Age, years	Severity of condition according to respiratory support (n/N (%))	Anakinra (A) dosage	Control (C)	Concomitant medication
Kyriazopoulou et al [10]	Inpatient Multicenter in Greece and Italy; randomized, double-blinded, placebo-controlled	N ^{total} : 594 n ^{Anakinra} : 405 n ^{Control} : 189	Mean (SD): A: 62 (11.4) C: 61.5 (11.3)	no supplemental oxygen: A: 39/405 (10); C: 11/189 (6) low or high flow supplemental oxygen: A: 366/405 (90); C: 178/189 (94) suPAR ≥ 6 ng/ml	100 mg (s.c.) daily for 7–10 days	Placebo: 0.9% sodium chloride daily for 7–10 days	Any glycopeptide A: 24 (5.9%); C: 19 (10.1%) Azithromycin A: 76 (18.8%); C: 35 (18.5%) β-lactamase inhibitors A: 23 (5.7%); C: 10 (5.3%) Ceftaroline A: 75 (18.5%); C: 32 (16.9%) Ceftriaxone A: 155 (38.3%); C: 85 (45.0%) Dexamethasone enrollment A: 342 (84.4%); C: 168 (88.9%) Linezolid A: 45 (11.1%); C: 22 (11.6%) Low-molecular-weight heparin A: 385 (95.1%); C: 175 (92.6%) Piperacillin/tazobactam A: 64 (15.8%); C: 36 (19.0%) Remdesivir A: 298 (73.6%); C: 141 (74.6%) Respiratory fluoroquinolone A: 53 (13.1%); C: 24 (12.7%)

Table 1 (continued)

References	Setting; Study-design	Participants allocated, n	Age, years	Severity of condition according to respiratory support (n/N (%))	Anakinra (A) dosage	Control (C)	Concomitant medication
Tharaux [40]	Inpatient Multicenter in France; randomized, controlled, open-label	$N^{\text{total}} = 114$ $n^{\text{Anakinra}} = 59$ $n^{\text{Control}} = 55$	Median (IQR): A: 67 (55.5–74.3) C: 64.9 (59.5–78.3)	Low flow supplemental oxygen A: 59/59 (100) C: 55/55 (100)	2 × 200 mg (i.v.) daily on days 1–3, followed by 2 × 100 mg (i.v.) daily on day 4 and 100 mg (i.v.) daily on day 5 In the absence of improvement (reduction in oxygen requirement by > 50%) after 3 days, decision by practitioner: 2 × 200 mg(i.v.) daily d4–6, then 2 × 100 mg (i.v.) d7, then 1 × 100 mg (i.v.) d8	Standard of Care: Antibiotics, antiviral meds, corticosteroids, vasopressors, anticoagulants (practitioner's choice)	Anticoagulants A: 33 (59%); C: 29 (53%) Azithromycin A: 11 (19%); C: 14 (25%) Dexamethasone A: 1 (2%); C: 0 (0%) Hydroxychloroquine A: 2 (3%); C: 4 (7%) Lopinavir–ritonavir or lopinavir A: 1 (2%); C: 2 (4%) Other glucocorticoids A: 6 (10%); C: 8 (15%)

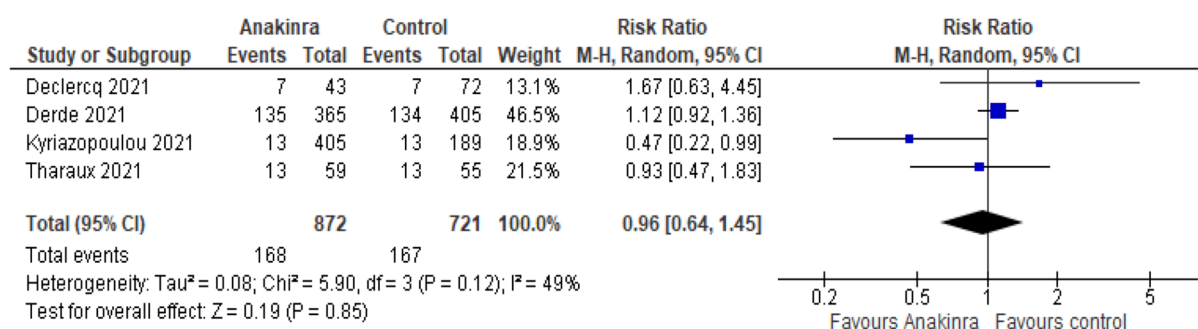
^a Characteristics of the patients at baseline available for A: 43, C: 72; outcomes partially available for A: 44, C: 74

^b Without differentiation between low and high flow

IMV invasive mechanical ventilation, s.c. subcutaneously, i.v. intravenously, ICU intensive care unit, ECMO Extracorporeal membrane oxygenation, suPAR soluble urokinase plasminogen activator receptor

Table 2 Summary of findings

Anakinra compared to placebo or standard care alone on clinical outcomes in SARS-CoV-2 patients					
Outcomes Time frame of absolute effects	Absolute effects from study(ies) (95% CI)			Relative effect 95% CI	Quality of the evidence (GRADE)
	Placebo or Standard Care Alone	Anakinra	Difference with Anakinra		
28-day mortality	232 per 1000	223 per 1000 (148 to 336)	9 Fewer per 1000 (84 Fewer—104 More); 4 studies; 1593 participants	0.96 (0.64 to 1.45)	⊕ ⊕ ⊕ ⊕ LOW Due to serious inconsistency, Due to serious imprecision
60-day mortality	125 per 1000	233 per 1000 (102 to 526)	108 More per 1000 (23 Fewer—401 More); 1 study; 115 participants	1.86 (0.82 to 4.21)	⊕ ⊕ ⊕ ⊕ LOW Due to very serious imprecision
Mortality at hospital discharge	331 per 1000	404 per 1000 (254 to 635)	73 More per 1000 (76 Fewer—305 More); 2 studies; 889 participants	1.22 (0.77 to 1.92)	⊕ ⊕ ⊕ ⊕ MODERATE Due to serious imprecision
Clinical worsening: new need for invasive mechanical ventilation or death (at day 28)	138 per 1000	95 per 1000 (42 to 215)	43 Fewer per 1000 (95 Fewer—77 More); 2 studies; 709 participants	0.69 (0.31 to 1.56)	⊕ ⊕ ⊕ ⊕ LOW Due to serious inconsistency, Due to serious imprecision
Clinical worsening: new need for invasive mechanical ventilation or death (at day 28) in patients with suPAR ≥ 6 ng/ml	127 per 1000	62 per 1000 (36 to 105)	65 Fewer per 1000 (90 Fewer—22 Fewer); 1 study; 594 participants	0.49 (0.29 to 0.83)	⊕ ⊕ ⊕ ⊕ MODERATE Due to serious imprecision
Clinical improvement: discharged without clinical deterioration (at day 28)	744 per 1000	766 per 1000 (654 to 900)	22 More per 1000 (89 Fewer—156 More); 3 studies; 823 participants	1.03 (0.88 to 1.21)	⊕ ⊕ ⊕ ⊕ LOW Due to serious inconsistency, Due to serious imprecision
Serious adverse events	241 per 1000	246 per 1000 (163 to 368)	5 More per 1000 (77 Fewer—128 More); 3 studies; 823 participants	1.02 (0.68 to 1.53)	⊕ ⊕ ⊕ ⊕ LOW Due to serious inconsistency, Due to serious imprecision
Adverse events (any grade)	520 per 1000	556 per 1000 (436 to 712)	36 More per 1000 (83 Fewer—192 More); 2 studies; 229 participants	1.07 (0.84 to 1.37)	⊕ ⊕ ⊕ ⊕ LOW Due to serious risk of bias, Due to serious imprecision
Adverse events (grades 3–4)	333 per 1000	373 per 1000 (223 to 616)	40 More per 1000 (110 Fewer—283 More); 1 study; 115 participants	1.12 (0.67 to 1.85)	⊕ ⊕ ⊕ ⊕ VERY LOW Due to serious risk of bias, Due to very serious imprecision

**Fig. 2** Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding all-cause mortality at up to day 28. *M-H* Mantel-Haenszel

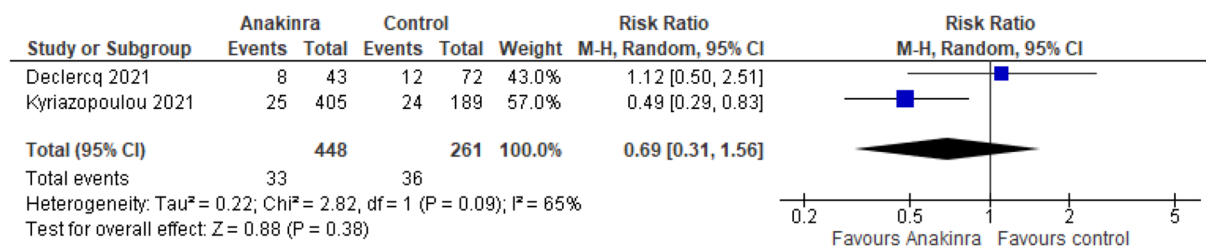


Fig. 3 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding worsening of clinical status. M-H Mantel-Haenszel

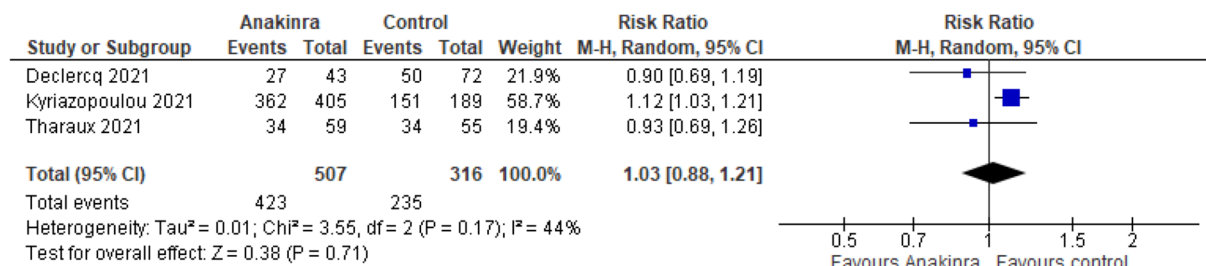


Fig. 4 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding improvement of clinical status. M-H Mantel-Haenszel

reason for downgrading was serious imprecision due to data from only one study.

Improvement of clinical status

Discharged without clinical deterioration

Three studies reported this outcome at day 28 for 823 participants (Fig. 4). We found that treatment with Anakinra has no effect on being discharged without clinical deterioration at day 28 (RR 1.03, 95% CI 0.88–1.21; RD 22 more per 1000, 95% CI 89 fewer to 156 more; 3 studies, 823 participants; $I^2 = 44\%$; low certainty of evidence). Our reasons for downgrading were serious inconsistency due to inconsistent direction and widely varying point estimates and serious imprecision due to wide CIs and that the CI includes both benefits and harms.

Quality of life

We did not find any data for this outcome.

Safety outcomes

Serious adverse events

Three studies reported this outcome for 823 participants (Additional file 6: Fig. S6). We found that treatment with Anakinra probably has little or no difference on SAE compared to standard care plus/minus placebo (RR 1.02, 95% CI 0.68–1.53; RD 5 more per 1000, 95% CI 77 fewer to 128 more; 3 studies, 823 participants; $I^2 = 56\%$; low certainty of evidence). The reasons for downgrading were serious inconsistency due to inconsistent direction and

widely varying point estimates and serious imprecision due to wide CIs and that CI includes both benefits and harms.

Adverse events

Two studies reported any AE for 229 participants (Additional file 6: Fig. S7). We found that treatment with Anakinra may have little or no difference on AE (RR 1.18, 95% CI 0.78–1.76; RD 36 more per 1000, 95% CI 83 fewer to 192 more; two studies, 229 participants; $I^2 = 0\%$; low certainty of evidence). The reasons for downgrading were serious risk of bias due to lack of blinding and serious imprecision due to wide CIs and the fact that CI includes both benefits and harms.

One study reported AE grades 3–4 for 115 participants (Additional file 6: Fig. S8). We found that treatment with Anakinra may have little or no difference on AE (RR 1.12, 95% CI 0.67–1.85; RD 40 more per 1000, 95% CI 110 fewer to 283 more; one study, 115 participants; I^2 not applicable; very low certainty of evidence). The main reason for downgrading was serious risk of bias due to lack of blinding and very serious imprecision due to wide CIs, few patients and data from only one study.

Discussion

Five RCTs comparing Anakinra treatment with placebo or standard care alone in 1,627 hospitalized patients with SARS-CoV-2 infection were included. There was

variability regarding setting, Anakinra dosage and duration as well as concomitant medication.

Regarding the primary outcome, we found that Anakinra makes little or no difference to all-cause mortality at up to day 28 compared to placebo or standard care alone. Regarding secondary outcomes, the meta-analysis showed no benefit for Anakinra with respect to clinical status, quality of life, SAEs and AEs.

The Cochrane review of Davidson et al. [55], which examined two RCTs [10, 40] for all-cause mortality, came to a similar conclusion as our meta-analysis. In addition, our findings regarding clinical improvement are also supported by Davidson et al. [55]. Regarding the outcome clinical worsening, neither of us found an effect of Anakinra, but because different studies were included in the meta-analyses, the results are only comparable to a limited extent in terms of content. Davidson et al. [55] performed meta-analysis with the studies of Kyriazopoulou et al. [10] and Tharaux et al. [40], while we included the studies of Kyriazopoulou et al. [10] and Declercq et al. [28] in our meta-analysis.

Contrary to our review, a meta-analysis published in *Lancet Rheumatology* showed a significant reduction in mortality in patients with moderate to severe COVID-19 receiving Anakinra compared to standard of care with or without placebo [54]. However, this review included mostly observational studies and only one RCT. The systematic review of Somagutta et al. [56], which analysed severe cases of COVID-19, concluded that the use of Anakinra for patients with COVID-19 was associated with a significantly low mortality rate and mechanical ventilation compared with standard care alone. Though, this review included only one RCT and mainly observational studies, case series and case reports.

Regarding clinical improvement by day 28, our analysis detected a favourable effect of Anakinra when considering only one study using biomarker-guided therapy ($\text{suPAR} \geq 6 \text{ ng/ml}$) [10]. As this biomarker was not determined in any other study, a comparison to other study data as well as to a subgroup with non-elevated suPAR is not possible. Thus, the role of the elevated suPAR biomarker as a determinant of response to Anakinra therapy is uncertain. Despite this result, current treatment recommendations [9] are often based on the beneficial effect reported by Kyriazopoulou et al. [10]. Therefore, it is of clinical importance to investigate the role of suPAR as biomarker for the treatment of COVID-19 with Anakinra.

Our search for systematic reviews and meta-analysis showed that most systematic reviews analysing the effect of Anakinra in adult hospitalized COVID-19 patients include mainly observational studies [54, 56–63].

However, to make evidence-based recommendations, it is of great interest that RCTs are performed because of their higher level of evidence.

Limitations

The outcomes of interest were revised and partially changed compared to the protocol, due to new knowledge regarding their clinical relevance. Moreover, one of the included studies is a preprint, which has not yet been peer-reviewed and could change until publication. Due to the selected inclusion criteria only few studies were included. Furthermore, the approach of each study regarding their inclusion criteria was heterogeneous. Therefore, meta-analysis was not always possible. In addition, the analyses conducted compare results of studies that differ regarding their patient population, especially disease severity, degree of oxygenation impairment, biomarkers, concomitant medication, Anakinra dosage studied and duration of therapy. However, subgroup analysis was not possible, due to the fact that the data needed for analyses were not available.

Conclusion

Anakinra has no effect on adult hospitalized patients with SARS-CoV-2 infection regarding mortality, clinical improvement or worsening as well as on safety outcomes compared to placebo or standard care alone. However, there might be a potential benefit of therapy with Anakinra in hospitalized patients with COVID-19 with low-flow/high-flow oxygen therapy and $\text{suPAR} \geq 6 \text{ ng/ml}$ regarding the need for invasive mechanical ventilation or death by day 28.

Abbreviations

ZBS	Centre for Biological Threats and Special Pathogens
CCSR	Cochrane Central Register of Controlled Trials
RCT	Randomized controlled trials
EMA	European Medicines Agency
IL-1	Interleukin-1 receptor antagonist
suPAR	Soluble urokinase plasminogen activator receptor
RA	Rheumatoid arthritis
ICTRP	International clinical trials registry platform
SAE	Serious adverse events
AE	Adverse events
MD	Mean difference
CI	Confidence interval
RR	Risk ratio
HR	Hazard ratio
IMV	Invasive mechanical ventilation
ICU	Intensive care unit
i.v.	Intravenously
s.c.	Subcutaneously
ECMO	Extracorporeal membrane oxygenation
RD	Risk difference

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40001-023-01072-z>.

Additional file 1. Differences to protocol.

Additional file 2. Search strategies.

Additional file 3. Records excluded during full-text screening.

Additional file 4. Characteristics of included studies.

Additional file 5. Risk of bias assessment.

Additional file 6. Meta-analyses of Anakinra versus control.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KD, AM and MIM. The first draft of the manuscript was written by KD and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this review are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have disclosed that they do not have any competing interests.

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Supplementary Information No 1 Differences to protocol

1. Due to the fact that ‘no treatment’ is only applicable within the ambulatory setting, we chose to change the review question into the following: The objective of this systematic review is to assess the safety and effects of Anakinra compared to placebo or standard care alone on clinical outcomes in adult hospitalized patients with SARS-CoV-2 infection.
2. Due to changes of outcomes within the CEOsys project, the outcome set was changed on the basis of clinical relevance. The following outcomes were used in the current publication:

Prioritised outcomes

- All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up.
- Clinical status at day 28, day 60, and up to longest follow-up, including:
 - worsening of clinical status:
 - participants with clinical deterioration (new need for invasive mechanical ventilation) or death;
 - improvement of clinical status:
 - participants discharged alive. Participants should be discharged without clinical deterioration or death.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available.

Safety outcomes

- Serious adverse events during the study period, defined as number of participants with any serious adverse event (serious as defined according to CTCAE (Common Terminology Criteria for Adverse Events)).
- Adverse events (any grade, grade 3-4) during the study period, defined as the number of participants with any adverse event.

Supplementary Information No 2 Search strategies

Cochrane COVID-19 Study Register

Search string:

Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Anril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor"

Study characteristics:

- 1) "Intervention assignment": "Randomised" OR "unclear" OR
- 2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover"
- 3) "Study type": "Interventional" AND "Study design": "Unclear"
- 4) "Study type": "Adaptive/Platform"

= 92 references

WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject:

(Anakinra OR "IL1 Febrile Inhibitor" OR "Interleukin 1 Inhibitor" OR Anril OR Kineret OR "Interleukin 1 Receptor Antagonist" OR "IL-1Ra" OR "IL-1 Inhibitor" OR "IL 1Ra" OR "IL 1 Inhibitor") AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

= 147 references

Supplementary Information No 3 Records excluded during full-text screening

Author	Year	Title	Type	Reason for exclusion in full-text screening
Assistance Publique Hopitaux De Marseille, NCT04424056	2020	A Trial Using ANAKINRA, TOCILIZUMAB Alone or in Association With RUXOLITINIB in Severe Stage 2b and 3 of COVID19-associated Disease	Trial registry	Wrong intervention
Kyriazopoulou et al. Preprint	2020	Anakinra To Prevent Respiratory Failure In COVID-19	Preprint	Wrong study design
Kyriazopoulou et al.	2021	An open label trial of anakinra to prevent respiratory failure in COVID-19	Journal publication	Wrong study design
University of Manchester EUCTR2020-001636-95-GB	2020	Does subcutaneously(SC) administered of anakinra achieve good penetration in blood and result in reduce inflammation in patients with SARS-CoV-19?	Trial registry	Wrong comparator
Swedish Orphan Biovitrum EUCTR2020-001167-93	2020	A clinical trial investigating efficacy and safety of emapalumab and anakinra in patients with Coronavirus disease (COVID-19)	Trial registry	Wrong comparator
Kaplanski G, Bontemps D, Esnault P, et al.	2020	Combined Anakinra and Ruxolitinib treatment to rescue extremely ill COVID-19 patients: a pilot study	Journal publication	Wrong comparator
Swedish Orphan Biovitrum NCT04324021	2020	Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection	Trial registry	Trial terminated
University Hospital Tours NCT04364009	2020	Anakinra for COVID-19 Respiratory Symptoms	Trial registry	Trial terminated
Centre Hospitalier Intercommunal de Toulon La Seyne sur Mer NCT04366232	2020	Efficacy of Intravenous Anakinra and Ruxolitinib During COVID-19 Inflammation (JAKINCOV)	Trial registry	Trial terminated
CHRU de TOURS EUCTR2020-001734-36	2020	Efficacy and safety of ANAKINRA during Adult COVID-19 with Aggravating respiratory symptoms: a multicenter open-label controlled randomized trial	Trial registry	Trial terminated
Weill Medical College of Cornell University, NCT04603742	2020	Anakinra, COVID-19, Cytokine Storm	Trial registry	Registry withdrawn

Supplementary Information No 4 Characteristics of included studies

Declercq 2021 Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
Randomized controlled trial, 2x2 factorial design, open-label, Inpatient	16 hospitals in Belgium	Patients: N^{Total}: 118 (with other interventions: 342) A: n = 43¹ C: n = 72 Excluded: Not reported for Anakinra and control only <u>Follow-up:</u> 10-20 weeks after randomization Inclusion criteria: - Recent infection with COVID-19 - Presence of hypoxia - Signs of cytokine release syndrome - Chest x-ray and/or CT scan showing bilateral infiltrates within last 2 days - Admitted to specialized COVID-19 ward or an ICU ward taking care of COVID-19 patients ≥ 18 years - Male or female - Women of childbearing potential must have a negative serum pregnancy test pre-dose on day 1 - Willing and able to provide informed consent or legal representative willing to provide informed consent Exclusion criteria: - Patients with known history of serious allergic reactions, including anaphylaxis to any of the study medications, or any component of the product - Mechanical ventilation > 24h at randomization - Patient on ECMO at time of screening - Clinical frailty scale above 3 - Active bacterial or fungal infection - Unlikely to survive beyond 48 h - Neutrophil count below 1500 cells/microliter - Platelets below 50.000/microliter - Patients enrolled in another investigational drug study	Anakinra 1x/day 100mg subcutaneously for 28 days or until hospital discharge on top of standard of care If glomerular filtration rate <30 ml/min per 1,73 m2, the dosing was lowered to 100mg once every other day.	Standard of Care (not specified)	Primary outcome: <u>Time to clinical improvement</u> Number of deaths A: 10/44 (23%) C: 9/74 (12%) Secondary outcomes: - Median time until discharge (IQR) A: 14 (9-37) C: 12 (10-20) - Median time until independence from supplemental oxygen or discharge A: 14 (8-20) C: 11 (10-15) - Median time until independence from invasive ventilation A: <50% reached event C: 54 (6-.) - Median time until first use of high-flow oxygen device, ventilation or death A: <50% reached event C: <50% reached event - Number of days in hospital A: 20 (16-25) C: 18 (15-22) - Number of days in ICU A: 12 (7-21) C: 9 (6-14)	No shortening of time to clinical improvement or improvement of supportive endpoints when given early in disease course of hypoxia patients with COVID-19 with evidence of CRS. No increase in infectious adverse events or other safety concerns associated with use of Anakinra. Comments: <u>Limitations:</u> - Open-label design - Standard of care could differ among centres and did change during the course of the trial - small sample size - total number of patients screened for eligibility not registered in all centres - decision to exclude patients unlikely to survive beyond 48h made by the individual enrolling physician on clinical grounds without objective criteria beyond the use of a frailty scoring index

Supplementary Information No 4 Characteristics of included studies

Declercq 2021 Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		– Patients on high dose systemic steroids – Patients on immunosuppressant or immunomodulatory drugs – Patients on current anti-IL1 or anti-IL6 treatment – Signs of active tuberculosis – Serum transaminase levels >5times upper limit of normal, unless there are clear signs of cytokine release syndrome – History of (non-iatrogenic) bowel perforation or diverticulitis – Pregnant or breastfeeding females Demographics: <u>Age, median (IQR):</u> A: 65 (54 - 70) C: 63 (56 - 73) <u>Male, n (%)</u> A: 37 (86) C: 53 (74) Severity of condition according to respiratory support (n/N (%)): IMV: A: 8/43 (19); C: 9/72 (13) non-IMV: A: 16/43 (37); C: 23/72 (32) supplemental oxygen only²: A: 19/43 (44); C: 39/72 (54) Not requiring supplemental oxygen: A: 0/43 (0); C: 1/72 (1)				
¹ characteristics of the patients at baseline available for A: 43, C: 72; outcomes partially available for A: 44, C: 74 ² without differentiation between low and high flow						
Derde 2021 The REMAPCAP Investigators: Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. medRxiv [Preprint] 2021.06.18.21259133; doi: https://doi.org/10.1101/2021.06.18.21259133						
Design	Study period and place	Participants	Intervention (Anakinra, A)	Control (C)	Outcomes	Conclusion of study authors
Randomized controlled trial,	19.04.2020 - 10.04.2021,	Patients: screened: n = 13,718 randomised to a COVID-19 Immune	Anakinra (A) 300mg IV loading dose	Standard of Care (not specified)	Primary outcome¹: In-hospital death, n (%)	“Anakinra is not effective in this population” Comments:

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
open-label, Inpatient, (Preprint)	127 sites (4 sites for Moderate state (3 UK, 1 Australia) & 123 sites for Severe State (110 UK, 11 Netherlands, 3 Ireland, 2 Australia, 2 New-Zealand, 1 Canada, 1 Finland, 1 Italy, 1 Saudi-Arabia))	Modulation Domain intervention: n=2,279 N= 779 A: n = 373 C: n = 406 Excluded: A: 13 C: 12 <u>Follow-up:</u> - 21 d for primary outcome and 90d for secondary outcomes Inclusion criteria: - > 18 years - within 24 hours of receiving respiratory or cardiovascular organ support in an ICU - suspected or microbiologically confirmed COVID-19 Exclusion criteria: - Patient has already received any dose of one or more of any form of anakinra during this hospitalization or is on long-term therapy with this agent prior to this hospital admission - Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization - Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected COVID-19 infection, where the protocol of that trial requires ongoing administration of study drug - The treating clinician believes that participation in the domain would not be in the best interests of the patient - Known hypersensitivity to anakinra - Known hypersensitivity o proteins produced by E. coli - Known or suspected pregnancy Demographics: <u>Age, mean (SD)</u> Severe state: A: 59.8 (11.9) C: 61.1 (12.9)	100mg every 6 hours for 14 days or until for > 24 h free from IMV or discharge from ICU. creatinine clearance <30ml/min or receiving renal replacement therapy: dosing interval increased to 12 h		A: 145/365 (39.7) C: 150/406 (36.9) Secondary outcomes: 90-day mortality, adjusted HR – mean (SD) A: 1.15 (0.16) C: 1 Progression into intubation, ECMO or death, n (%) A: 122/228 (53.5) C: 147/276 (53.3) Time to ICU discharge, adjusted HR – mean (SD) A: 1.10 (0.12) C: 1 Time to hospital discharge, adjusted HR – mean (SD) A: 1.05 (0.12) C: 1	<u>Limitations:</u> – open-label design

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		Moderate State: A: 36.0 (17.0) C: 67.0 (13.7) <u>Male, n (%)</u> Severe state: A: 269 (72.1) C: 285 (70.2) Moderate State: A: 1 (50.0) C: 1 (33.3) Severity of condition according to respiratory support (n/N (%)): None / supplemental oxygen only A: 1/373 (0.3) C: 2/406 (0.5) High-flow nasal cannula A: 101/373 (27.1) C: 110/406 (27.1) Non-invasive ventilation only A: 133/373 (35.7) C: 171/406 (42.1) Invasive mechanical ventilation A: 138/373 (37.0) C: 122/406 (30.0) ECMO A: 0/373 (0.0) C: 1/406 (0.2)				
¹ The primary outcome was an ordinal scale that is a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support (Days free from organ support in survivors, median (IQR))						
Kharazmi 2021						
Kharazmi AB, Moradi O, Haghighi M, et al: A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19. <i>Immun Inflamm Dis</i> 2022; 10:201–08						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
Randomized controlled trial, open-label, Inpatient,	Iran, May 2020 to July 2020	Patients: Screening: n = 72 Patients: n = 30 A: n = 15 C: n = 15 Excluded: n = 42	Anakinra 1x/day 100mg IV until discharge or a maximum of 14 days	Standard of Care (not specified)	Primary outcome: <u>Need for invasive mechanical ventilation</u> Secondary outcomes:	“Anakinra is effective in improving the respiratory condition and significantly reduces the need for invasive mechanical ventilation in patients with severe COVID-19. “

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		<u>Follow-up:</u> for the primary outcome: until endotracheal intubation due to hypoxemia for the secondary outcomes: until hospital discharge Inclusion criteria: – confirmed diagnosis of COVID-19 based on reverse transcriptase-polymerase chain reaction – admitted to ICU – > 18 years old – elevated C-reactive protein (CRP) levels – oxygen saturation $\leq$ 93% measured using a peripheral capillary pulse oximeter – fever (core temperature of 37.8°C or more), or cough or shortness of breath, and PaO₂/FiO₂ less than 300 Exclusion criteria: – Patients who had positive results for tuberculosis (i.e., positive Mendel–Mantoux or QuantiFERON test), – viral hepatitis B or C – hemoglobin < 7.5 g/dl – platelet count < 100,000 cells/μl – serum glutamic–oxaloacetic transaminase or serum glutamic–pyruvic transaminase > five upper limits of normal – untreated active infection – previous administration of anakinumab or anakinra Demographics: <u>Age. (SD)</u> A: 49.25 $\pm$ 19.12 C: 59.00 $\pm$ 1.79 <u>Male. (%)</u> A: 8% C: 7%			Hospital length of stay, Median (IQR) A: 10 (5) C: 28 (15) ICU length of stay, Median (IQR) A: 5 (3) C: 16 (19) <u>Seven categories ordinal scale, n (%)</u> Death A: 5 (33.3) C: 7 (46.7) p = .456 Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation. A: 0 (0) C: 2 (13.3) P = .483 Hospitalized, on non-invasive ventilation or high flow oxygen A: 0 (0) C: 1 (6.7) P = 1.000 Hospitalized, requiring low flow supplemental oxygen A: 0 (0) C: 0 (0) P = 1.000 Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise) A: 0 (0) C: 0 (0) P = 1.000	“The reduction was observed in hospitalization duration, which makes the medication an effective immunomodulatory agent to combat cytokine storm.” Comments: <u>Limitations:</u> – Open label design – Small sample size

Supplementary Information No 4 Characteristics of included studies

Declercq 2021 Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		Severity of condition according to respiratory support (n/N (%)): IMV or ECMO: A: 2/15 (13); C: 3/15 (20) non-IMV or high flow oxygen: A: 10/15 (67); C: 6/15 (40) low flow supplemental oxygen only: A: 3/15 (20); C: 6/15 (40)			Hospitalized, not requiring supplemental oxygen—no longer required ongoing medical care. A: 0 (0) C: 0 (0) P = 1.000 Not hospitalized A: 10 (66.7) C: 5 (33.3) P = .143 Survival for included patients on day 14	
Kyriazopoulou 2021 Kyriazopoulou E, Poulakou G, Milonis H, et al: Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. <i>Nat Med</i> 2021; 27:1752–1760						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
Randomized controlled trial; double-blinded, placebo-controlled, Inpatient	23 December 2020 to 31 March 2021 37 study sites (29 in Greece and eight in Italy)	Patients: Screening: n=1,060 Patients: n=606 A: n=405 C: n=189 Excluded: n=454 <u>Follow-up:</u> until hospital discharge Inclusion criteria: - adult patients of either sex - for women, unwillingness to remain pregnant during the study period - confirmed infection by SARS-CoV-2 by molecular test - findings in chest X-ray or chest computed tomography compatible with lower respiratory tract infection - need for hospitalization - plasma suPAR $\geq 6 \text{ ng ml}^{-1}$ Exclusion criteria: - any stage IV malignancy	Anakinra 1x/day 100mg subcutaneously at a final volume of 0.67 ml for 7-10 days	Placebo 1x/day 0.67 ml of 0.9% sodium chloride	Primary outcome: <u>11-point WHO-CPS at day 28, n (%)</u> Fully recovered PCR– A: 204 (50.4) C: 50 (26.5) Asymptomatic PCR+ A: 40 (9.9) C: 6 (3.2) Symptomatic independent A: 93 (23.0) C: 74 (39.2) Symptomatic assistance needed A: 25 (6.2) C: 21 (11.1) Hospitalized with no need for oxygen A: 9 (2.2) C: 3 (1.6) Hospitalized with nasal/mask oxygen A: 8 (2.0)	“In conclusion, the SAVE-MORE trial showed that early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28.” Comments: <u>Limitations:</u> - the lack of enrollment of patients with critical COVID-19 - the difficulty for application of suPAR in all hospital settings - inclusion of patients with $\text{SuPAR} \geq 6 \text{ ng ml}^{-1}$ <u>Power-analysis:</u> “To replicate this primary effect size in the SAVE-MORE trial, and with a 90% power at the 5% significance level, a sample size of 200 was needed for the

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		- any do-not-resuscitate order - ratio or partial oxygen pressure to fraction of inspired oxygen less than 150 mmHg - need of NIV (CPAP or BPAP) or MV - any primary immunodeficiency - fewer than 1,500 neutrophils per mm³ - oral or intravenous intake of corticosteroids at a daily dose greater than or equal to 0.4 mg kg⁻¹ of prednisone for a period longer than the last 15 d - any anti-cytokine biological treatment, including JAK inhibitors, during the last 1 month - severe hepatic failure - end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis - pregnancy or lactation. Demographics (I/B1/B2): <u>Age, mean (SD)</u> A: 62 (11.4) C: 61.5 (11.3) <u>Male, n (%)</u> A: 236 (58.3) C: 108 (57.1) Severity of condition according to respiratory support (n/N (%)): no supplemental oxygen: A: 39/405 (10); C: 11/189 (6) low or high flow supplemental oxygen: A: 366/405 (90); C: 178/189 (94) suPAR ≥ 6 ng/ml			C: 10 (5.3) Need for HFO or NIV A: 1 (0.2) C: 1 (0.5) MV with P/F > 150 mmHg A: 1 (0.2) C: 1 (0.5) MV with P/F < 150 mmHg or vasopressors A: 5 (1.2) C: 4 (2.1) MV with P/F < 150 mmHg and vasopressors or hemodialysis or ECMO A: 6 (1.5) C: 6 (3.2) Dead A: 13 (3.2) C: 13 (6.9) Secondary outcomes: Median time to hospital discharge, d (IQR) A: 11 (7.8) C: 12 (8.5) P = 0.033 Median time of ICU stay, d (IQR) A: 10 (21) C: 14 (22) P = 0.026 At least one serious TEAE, n (%) A: 65 (16.0) C: 41 (21.7) P = 0.107 At least one non-serious TEAE, n (%) A: 335 (82.7) C: 156 (82.5) P = 1.00	placebo treatment arm and 400 for the anakinra treatment arm.”
Tharaux 2021						

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
The CORIMUNO-19 Collaborative Group: Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. <i>Lancet Respir Med</i> 2021; 9:295-304						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
Randomized controlled trial, open-label, Inpatient	08.04 – 26.04.2020 16 University hospitals in France	Patients: Screening: n = 153 Patients: n = 116 A: n = 59 C: n = 57 Excluded: n=37 Follow-up: 14d for primary outcome and 28d or 90d for secondary outcomes Inclusion criteria: - adult patients -confirmed SARS-CoV-2 infection (positive on real-time RT-PCR or chest CT scan typical of COVID-19 pneumonia, or both) with mild-to-moderate, severe, or critical pneumonia (ie, receiving oxygen at a flow of >3 L/min via mask or nasal cannula and a score of ≥5 points on the WHO Clinical Progression Scale [WHO-CPS] 10-point ordinal Scale -C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the hospital intensive care unit at the time of admission -mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but without ventilation assistance (eg, high-flow oxygen, non-invasive ventilation, or mechanical ventilation). Exclusion criteria: - known hypersensitivity to Anakinra or any of its excipients - pregnancy - current documented bacterial infection - an absolute neutrophil count of 1.0×10^9 per L or less	Anakinra 2 x 200 mg (i.v.) daily on days 1–3, followed by 2 x 100 mg (i.v.) daily on day 4 and 100 mg (i.v.) /daily on day 5 In the absence of improvement (reduction in oxygen requirement by >50%) after 3 days, decision by practitioner: 2x 200 mg(i.v.) daily d4-6, then 2x 100 mg (i.v.) d7, then 1x 100 mg (i.v.) d8	Standard of Care: Antibiotics, antiviral meds, corticosteroids, vasopressors, anticoagulants (practitioner's choice)	Co-primary outcomes: <u>The proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (ie, a score of ≥5 on the WHO-CPS)</u> A: 21/59 (36%) C: 21/55 (38%) <u>Survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14.</u> median posterior HR: 0.97 (90% CrI 0.62 to 1.52) <u>Non-invasive ventilation, mechanical ventilation or death up to day 14</u> A: 28 (47%; 95% CI 33 to 59) C: 28 (51%; 95% CI 36 to 62) <u>Mortality, at day 90</u> A: 16 (27%) C: 15 (27%) <u>Serious adverse events, n (%), p</u> Patients with at least one serious adverse event 27 (46%) / 21 (38%), 0.45 Patients with multiple serious adverse events 8 (14%) / 5 (9%),	“Anakinra did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia. Further studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19.” Comments: <u>Limitations</u> – No blinding – usual care could differ among centres and over time – small sample size – wide CrIs and CIs – no provision of an accurate measure of the ratio of partial pressure of oxygen to fractional concentration of oxygen in inspired air, because arterial blood gas measurements were not done – narrow segment of the COVID-19 patient population targeted (patients with a WHO-CPS score of exactly 5 points and requiring at least 3 L/min of oxygen without any ventilatory support regardless of inflammatory status)

Supplementary Information No 4 Characteristics of included studies

Declercq 2021						
Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
		- a platelet concentration of less than 50 G/L - serum aspartate aminotransferase or serum alanine aminotransferase of more than fivetimes the upper limit of normal - severe renal insufficiency defined by an estimated glomerular filtration rate of less than 30 mL/min. Demographics: <u>Age, median (IQR):</u> 66 (59 - 76) A: 67 (55.5 –74.3) C: 64,9 (59.5 –78.3) <u>Male, n</u> 80 (70%) Severity of condition according to respiratory support (n/N (%)): Low flow supplemental oxygen A: 59/59 (100) C: 55/55 (100)			Secondary outcomes: - clinical status assessed with the WHO-CPS at days 4, 7, and 14; <u>Overall survival at days 14, 28, and 90</u> Mortality at day 14 A: 9 (15%) C: 13 (24%) Adjusted HR: 0.56 (95% CI 0.23 to 1.39) Mortality at day 28 A: 13 (22%) C: 13 (24%) Adjusted HR: 0.77 (95% CI 0.33 to 1.77) Mortality at day 90 A: 16 (27%) C: 15 (27%) Adjusted HR: 0.97 (95% CI 0.46 to 2.04) <u>time to discharge at day 28</u> A: 34 (58%) C: 34 (62%) Adjusted HR: 0.91 (95% CI 0.56 to 1.48) <u>Time to oxygen supply independency at day 28, n (%), adj. HR (95% CI)</u> 37 (63%) / 38 (69%), 1.01 (95% CI 0.64 to 1.61) <u>time to negative viral excretion</u> not assessed due to paucity of data	

Supplementary Information No 4 Characteristics of included studies

Declercq 2021 Declercq J, van Damme KFA, De Leeuw E, et al: Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. <i>Lancet Respir Med</i> 2021; 9:1427–38						
Design	Study period and place	Participants	Intervention	Control	Outcomes	Conclusion
					<u>biological factors (eg, C-reactive protein concentration)</u> <u>Adverse events, n (%), p</u> Patients with at least one adverse event 29 (49%) / 23 (42%), 0.46 Patients with multiple adverse events 19 (32%) / 14 (25%) Subgroup analysis: prespecified subgroup analysis according to antiviral drug use at baseline: too few patients were on antivirals at baseline to enable this analysis.	

Supplementary Information No 5 Risk of bias assessment

Table 1 Risk of bias analysis for 28-day mortality

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
28-day mortality	Declercq 2021	Low	Low	Low	Low	Low	Low
	Derde 2021	Low	Low	Low	Low	Low	Low
	Kyriazopoulou 2021	Some concerns due to baseline differences	Low	Low	Low	Low	Some concerns
	Tharaux 2021	Low	Low	Low	Low	Low	Low

Table 2 Risk of bias analysis for 60-day mortality

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
60-day mortality	Declercq 2021	Low	Low	Low	Low	Low	Low

Table 3 Risk of bias analysis for mortality time-to-event at day 28

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Mortality time-to-event, 28 day	Tharaux 2021	Low	Low	Low	Low	Low	Low
	Kyriazopoulou 2021	Some concerns due to baseline differences	Low	Low	Low	Low	Some concerns

Table 4 Risk of bias analysis for mortality time-to-event at day 90

Outcome	Study	Risk of Bias					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Mortality time-to-event, 90 day	Tharaux 2021	Low	Low	Low	Low	Low	Low
	Derde 2021	Low	Low	Low	Low	Low	Low

Table 5 Risk of bias analysis for mortality at hospital discharge

Outcome	Study	Risk of Bias					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Mortality at hospital discharge	Derde 2021	Low	Low	Low	Low	Low	Low
	Declercq 2021	Low	Low	Low	Low	Low	Low

Table 6 Risk of bias analysis for clinical worsening: new need for invasive mechanical ventilation or death at day 28

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Clinical worsening: new need for invasive mechanical ventilation	Declercq 2021	Low	Low	Low	Low	Low	Low
	Kyriazopoulou 2021	Some concerns due to baseline differences	Low	Low	Low	Low	Some concerns

Table 7 Risk of bias analysis for clinical improvement: patients discharged alive

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Clinical improvement: patients discharged alive	Declercq 2021	Low	Low	Low	Low	Low	Low
	Kyriazopoulou 2021	Some concerns due to baseline differences	Low	Low	Low	Low	Some concerns
	Tharaux 2021	Low	Low	Low	Low	Low	Low

Table 8 Risk of bias analysis for serious adverse events

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Serious adverse events	Declercq 2021	Low	Low	Low	Low	Low	Low
	Kyriazopoulou 2021	Some concerns due to baseline differences	Low	Low	Low	Low	Some concerns
	Tharaux 2021	Low	Low	Low	Low	Low	Low

Table 9 Risk of bias analysis for any adverse events

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Adverse events, any	Declercq 2021	Low	Low	Low	Some concerns due to lack of blinding	Low	Some concerns
	Tharaux 2021	Low	Low	Low	Some concerns due to lack of blinding	Low	Some concerns

Table 10 Risk of bias analysis for adverse events, grade 3-4

Outcome	Study	Risk of Bias Domain					
		Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Adverse events, grade 3-4	Declercq 2021	Low	Low	Low	Some concerns due to lack of blinding	Low	Some concerns

Supplementary Information No 6 Meta-analyses of Anakinra versus control

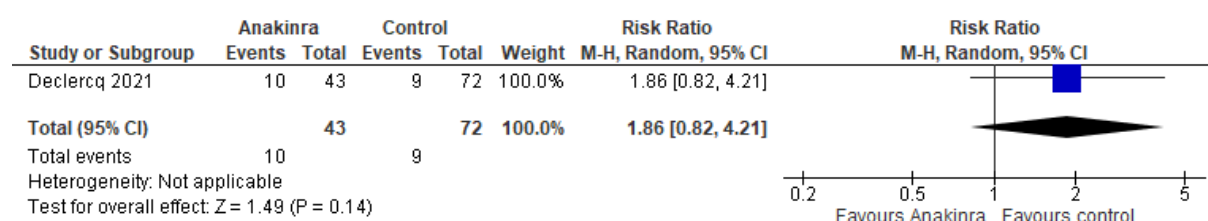


Fig. 1 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding 60-day mortality. M-H = Mantel-Haenszel.

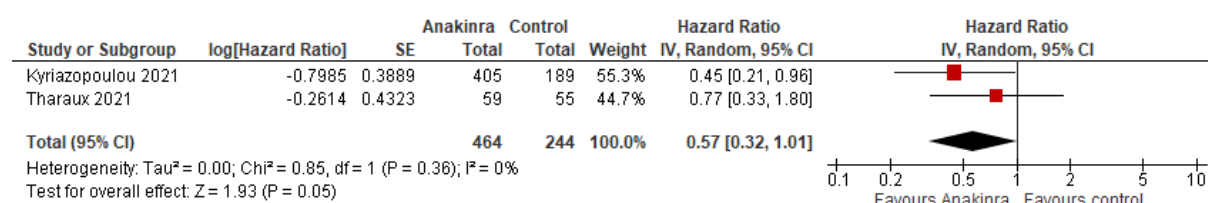


Fig. 2 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding 28-day mortality, time-to-event. M-H = Mantel-Haenszel.

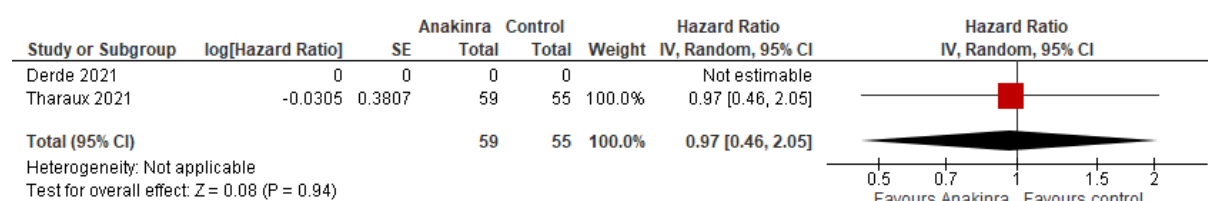


Fig. 3 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding 90-day mortality, time-to-event. M-H = Mantel-Haenszel.

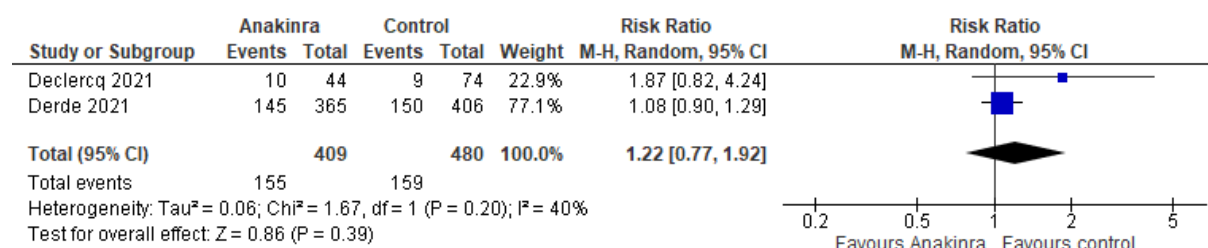


Fig. 4 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding mortality at hospital discharge. M-H = Mantel-Haenszel.

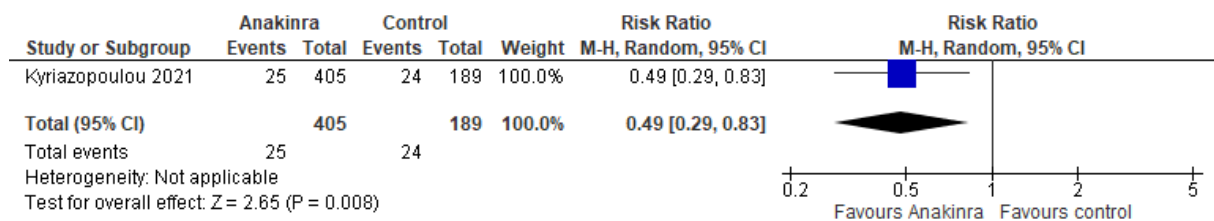


Fig. 5 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding worsening of clinical status in patients with suPAR ≥ 6 ng/ml. M-H = Mantel-Haenszel.

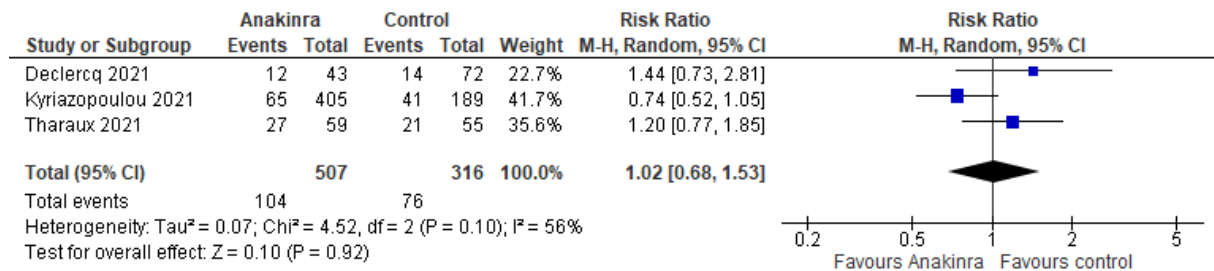


Fig. 6 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding serious adverse events. M-H = Mantel-Haenszel.

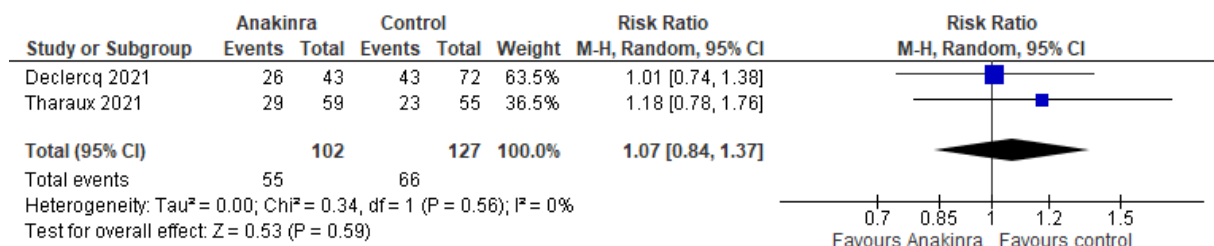


Fig. 7 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding any adverse events. M-H = Mantel-Haenszel.

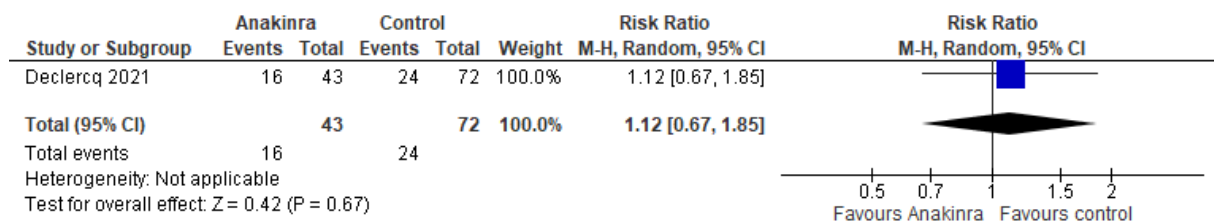


Fig. 8 Forest plot describing the difference between Anakinra compared to placebo or standard care alone regarding adverse events, grade 3-4. M-H = Mantel-Haenszel.



Effectiveness of antibiotic prophylaxis in polytrauma patients: a systematic review and meta-analysis

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Abstract

Purpose The use of antibiotic prophylaxis in trauma patients, particularly to prevent ventilator-associated pneumonia (VAP), is debated due to rising antibiotic resistance. Therefore, this systematic review evaluated the safety and effectiveness of antibiotic prophylaxis compared to placebo or standard care on clinical outcomes in adult polytrauma patients.

Methods We searched PubMed and the Cochrane Central Register of Controlled Trials to identify completed and ongoing studies from database inception to April 20, 2023. Eligible studies included systematic reviews and randomized controlled trials (RCTs) comparing antibiotic prophylaxis to placebo or standard care in adult polytrauma patients admitted to the intensive care unit (ICU).

Results Of 1237 identified records, three RCTs involving 256 patients ($n_{\text{antibiotics}} = 176$, $n_{\text{control}} = 165$, mean age 37.4 years, 81.6% male) were included. Antibiotic prophylaxis showed little or no effect on all-cause mortality compared to placebo or standard care (RR 1.01, 95% CI 0.55–1.85; RD 2 more per 1000, 95% CI -79 to 150; 2 studies, 209 participants; $I^2=0\%$; very low certainty of evidence).

Conclusion The results indicate that antibiotic prophylaxis has no significant effect on mortality and clinical status compared with placebo or standard care in adult polytrauma patients but may reduce the risk of VAP. However, the evidence is outdated and of very low certainty, with insufficient data to draw definitive conclusions regarding efficacy. Therefore, high-quality, up-to-date research is urgently needed to support clinical decision-making, and current interpretations should be treated with caution.

Keywords Antibiotic prophylaxis · Intensive care unit · ICU · Polytrauma · Multiple trauma

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Abbreviations

CI	Confidence interval
ICU	Intensive care unit
MD	Mean difference
MH	Mantel–Haenszel
MOF	Multiple organ failure
RCT	Randomized controlled trial
RD	Risk difference
RoB	Risk of bias
RR	Risk ratio
SDD	Selective decontamination of the digestive tract
SDSA	Selective decontamination locally in the subglottic area
SIRS	Systemic inflammatory response syndromes
SoC	Standard of care
VAP	Ventilator associated pneumonia

Introduction

Polytrauma, a condition characterized by severe multiple injuries, has long been a subject of concern in the medical community due to its association with a high mortality rate [1]. After 48 h of hospital stay, the mortality is particularly affected by systemic inflammatory response syndromes (SIRS), sepsis, and single and multiple organ failure (MOF) [2]. Among the many challenges faced by polytrauma patients, an increased risk of hemorrhage [3] and infections, such as ventilator associated pneumonia (VAP), is a significant threat to their recovery, as it is associated with an increased hospital stay, additional surgeries, and increased morbidity and mortality [4, 5, 6].

In this context, antibiotic prophylaxis is considered a possible solution [7, 8]. Selective decontamination of the digestive tract (SDD) is a prophylactic approach for patients in the intensive care unit (ICU). It has shown promise in reducing infection rates, especially in patients who require mechanical ventilation for over 48 h and often face the risk of developing VAP as a result of bacteria acquired during their hospital stay [9, 10, 11]. VAP and other acquired infections not only contribute to higher mortality rates but also pose significant challenges in treatment [8, 12].

However, the use of antibiotic prophylaxis remains a contentious topic in the medical field, especially in view of the alarming rise in antibiotic resistance. Antibiotic resistance is notably elevated within ICUs with outbreaks involving multidrug-resistant organisms [13, 14]. These challenges raise questions regarding the long-term effectiveness of antibiotic prophylaxis.

To provide current evidence on the efficacy of antibiotic prophylaxis, the objective of this systematic review is to assess the safety and effects of antibiotic prophylaxis

compared to placebo or standard care on clinical outcomes in adult polytrauma patients in the ICU.

Methods

This review is part of a guideline project that aimed to summarize the current evidence in the field of polytrauma to formulate specific recommendations. All studies that were conducted as part of this project used the same methodology, which was consented within the guideline group.

Eligibility criteria

We included studies comparing antibiotic prophylaxis to standard care or placebo in adult polytrauma patients admitted to the ICU who met the following inclusion criteria:

- Age of the included patients is ≥ 18 years.
- Polytrauma is defined as a simultaneous injury to multiple body regions or organ systems, at least one or more of which, in combination, is life-threatening.
- Randomized controlled trial (RCT) or systematic review that includes RCTs.
- Language of publication: English or German.
- No multiple publication without additional information.
- Publication accessible as full text.
- Comparison of use of validated handover tools with no use.

Search strategy

We conducted a systematic search developed by two experienced information specialists in PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception of each database to April 24, 2023. The details of the search strategy are provided in the Appendix No 1. In addition, we searched reference lists of the included studies to identify other potentially eligible studies.

Study selection

We imported the records from the systematic search into the Rayyan Systematic Review App (Rayyan, Cambridge, MA, USA). Three authors independently screened the titles and abstracts of the potential studies. Included full-text study publications were retrieved, imported into Microsoft Excel (Microsoft, Redmond, WA, USA), and screened by two authors independently. The reasons for exclusion of ineligible studies were recorded. Any disagreements were resolved through discussion or, if required, consultation with a third author if required.

Data collection process

One reviewer extracted study and outcome data into a customized data collection form developed in Microsoft Excel, which was checked by a second investigator. Any disagreements were resolved by discussion or by consulting a third review author if necessary.

The following data were obtained:

1. Study characteristics: authors, publication date, and study design.
2. Participants characteristics: number of included participants, gender, age.
3. Clinical outcomes: all-cause mortality (day 28, day 60, time to-event, and up to longest follow-up), clinical status (duration of mechanical ventilation, need for mechanical ventilation), length of stay, serious adverse events (SAE), adverse events (AE), infections, quality of life.

We transmitted the outcome data into a statistical software (RevMan 5.3, Cochrane, London, England). Missing data resulted in the exclusion of the study from the analysis of the missing outcomes.

Study risk of bias assessment

The risk of bias of the included studies was independently assessed by two authors using the Risk of Bias 2 (RoB 2) tool (Cochrane, London, England). This tool addresses five domains of bias (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results). The signaling questions of the tool were used to make a judgement according to the available options. We used the algorithms proposed in RoB 2 to assign each domain and the overall risk of bias to a level of bias: low risk of bias, some concerns, and a high risk of bias. Any disagreements between the reviewers were resolved by discussion or by involvement of another author.

Synthesis methods

Descriptive statistics were used to summarize demographics. Meta-analyses were performed only if the clinical and methodological characteristics of individual studies were sufficiently homogeneous. Data entry into the RevMan software was checked for accuracy by a second review author. Outcome data were pooled using the random-effects model, as we anticipated that the true effects would be related, but not the same, for the studies included in our review. For dichotomous data, we performed analyses using the

Mantel–Haenszel method under a random-effects model to report pooled risk ratios (RR) with 95% confidence intervals (CI). For continuous outcomes, we calculated mean differences with 95% CIs. Forest plots were used to summarize the effects of the individual studies. When data was lacking or incomplete for analysis, such information was reported narratively. A p -value of <0.05 was considered as statistically significant. The data were analyzed using the Cochrane methodology.

We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [15]. We considered $P < 0.1$ as significant for this test.

Certainty assessment

We used the GRADEpro Guideline Development Tool Software (McMaster University and Evidence Prime Inc., Hamilton, Ontario, Canada) to create a summary of findings table and evaluated the certainty of the evidence using the GRADE approach for interventions evaluated in RCTs.

Results

Study selection

The systematic search identified 1,145 records. After removing duplicates, we screened 1,086 records based on title and abstract; 1,021 studies did not meet the pre-specified inclusion criteria and were therefore excluded. We screened the full texts, trial register entries, and reference lists of the remaining 65 references. Sixty-two records were excluded (Fig. 1). Finally, three RCTs, published between 1976 and 2002, were included in our meta-analysis: Pichler [16], Quinio et al. [17] and Pneumatikos et al. [18].

Within this search, two different concepts of antibiotic prophylaxis in polytrauma patients were identified: selective decontamination and the use of penicillin and ampicillin. The corresponding studies were grouped and analyzed separately.

Study characteristics

Three RCTs [16, 17, 18] with a total of 256 participants (mean age 37.4 years, 81.6% male) with polytrauma met the criteria for inclusion and were analyzed in our meta-analysis. All included RCTs used a parallel-group design. Two studies compared selective decontamination with placebo [17, 18], whereas one study compared the usage of

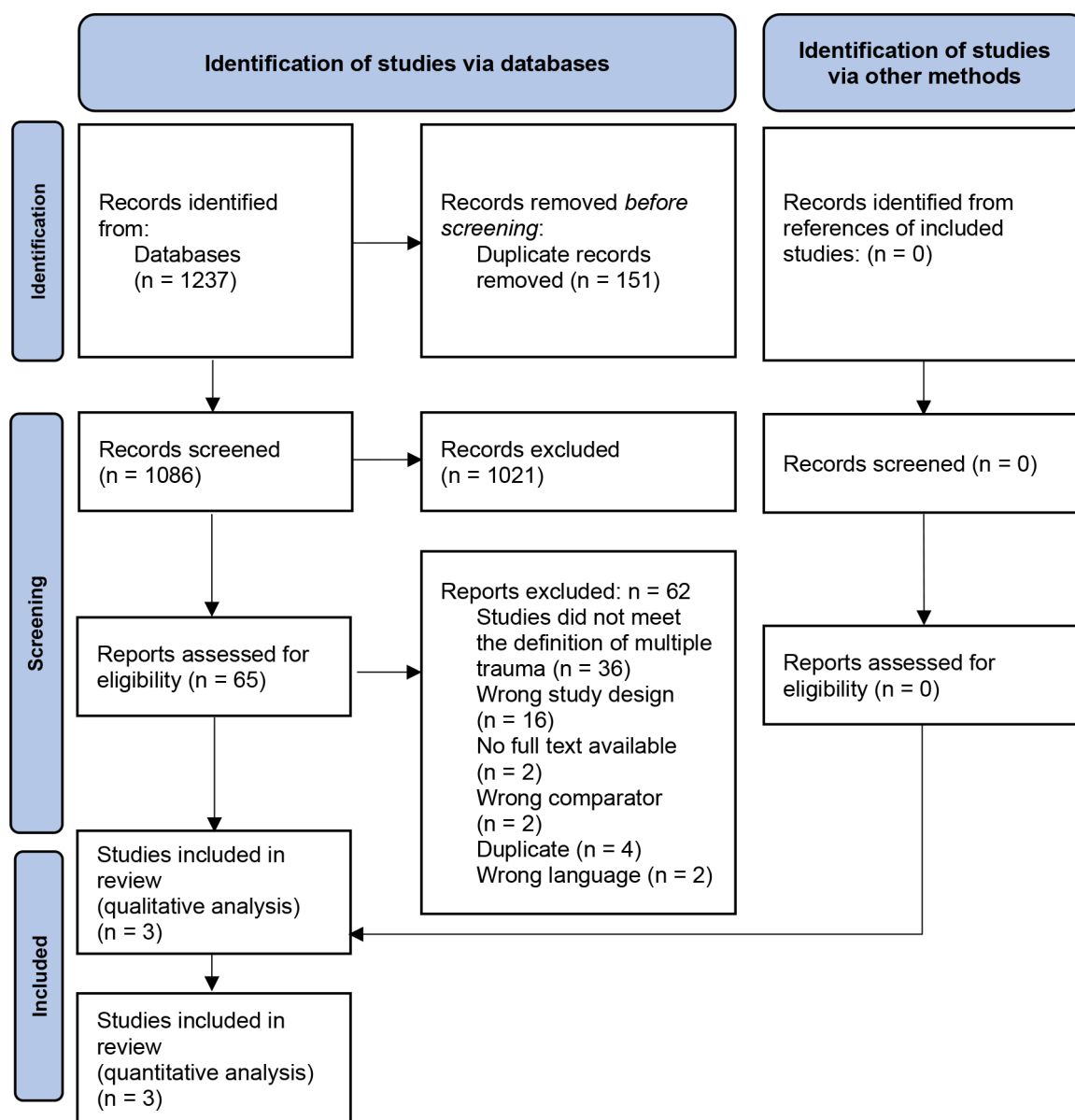


Fig. 1 Flowchart of the systematic review selection process

ampicillin and penicillin to standard of care [16]. The characteristics of the included studies are presented in Table 1.

Risk of bias in studies

The overall risk of bias among the three RCTs was high for all outcomes due to a lack of a pre-specified analysis plan, no - or no sufficient - information regarding an appropriate analysis method, concealment, or blinding.

Assessment of reporting bias was not possible as there were not enough studies included.

Results of individual studies

Antibiotic prophylaxis compared to placebo or standard care in adult polytrauma patients (Summary of findings Tables 2 and 3).

All-cause mortality

Ampicillin & penicillin vs. standard care

One study reported all-cause mortality for 47 participants (Fig. 2). We found that penicillin and ampicillin contribute little or not to all-cause mortality compared to standard care (RR 1.04, 95% CI 0.57–1.92; risk difference (RD) 18 more

Table 1 Study characteristics

Study (Year)	Study design	No of patients	Mean age $\pm$ SD (years)	Gender (m/f)	Intervention	Control
Quinio et al. (1996)	prospective, randomized, double-blind, placebo-controlled study	N=148 SDD: N=76 Placebo: N=72	SDD: 35.5 $\pm$ 16 Placebo: 33 $\pm$ 15	SDD: 66/10 Placebo: 62/10	Selective digestive decontamination (SDD): a suspension of colistin sulfate (polymyxin E) (10 mg/mL), gentamicin (8 mg/mL), and amphotericin B (50 mg/mL) instilled through the nasogastric tube (10 mL) and nares (2 mL in each) 4x/day. An oral gel made of carboxymethylcellulose containing 2% of the same antibiotics was also applied 4x/day with a glove in the oropharyngeal cavity; about 15 mL of gel was used for one application.	Placebo
Pichler (1976)	Randomized, clinical study	N=132 Antibiotics: N=69 Standard care: N=63	42.75	34/13	Antibiotic prophylaxis with 2 $\times$ 10 MegaE Natrium Penicillin G and 2 $\times$ 2 g Ampicillin	Standard care
Pneumatikos et al. (2002)	A prospective randomized, controlled, clinical study	N=61 SDSA: N=31 Placebo: N=30	SDSA: 39.1 $\pm$ 19.42 Placebo: 36.86 $\pm$ 19	SDSA: 24/77 Placebo: 23/76	Selective decontamination locally in the subglottic area (SDSA): continuous infusion of a suspension containing 73 mg polymyxin E, 73 mg tobramycin, and 500 mg amphotericin B in 500 mL 0.9 saline solution at an infusion rate of 2 mL/h in the subglottic area for the entire period of the study	Placebo

NR = Not reported

per 1000, 95% CI 197 fewer to 422 more; 1 study, 47 participants; very low certainty of evidence). The reason for downgrading was imprecision due to only one study, small number of participants, and a high risk of bias.

Selective decontamination vs. placebo

Two studies reported all-cause mortality for 209 participants (Fig. 3). We found that selective decontamination makes little or no difference to all-cause mortality compared to placebo (RR 1.01, 95% CI 0.55–1.85; risk difference (RD) 2 more per 1000, 95% CI 79 fewer to 150 more; 2 studies, 209 participants; $I^2=0\%$; very low certainty of evidence). The reasons for downgrading were a high risk of bias, indirectness due to inconsistent direction of point estimates, and imprecision due to the small number of participants.

Clinical status: duration of mechanical ventilation

Two studies reported duration of mechanical ventilation for 209 participants (Fig. 4). We found that selective decontamination makes little or no difference to duration of mechanical ventilation compared to placebo (mean difference (MD) 1.22 days higher, 95% CI 1.41 lower to 384 higher; 2 studies, 209 participants; $I^2=57\%$; very low certainty of evidence). The reason for downgrading was imprecision due to the small number of participants and a high risk of bias.

ICU length of stay

Two studies reported ICU length of stay for 209 participants (Fig. 5). We found that selective decontamination makes little or no difference to ICU length of stay compared to placebo (MD -3.43 days lower, 95% CI -10.58 lower to 3.73 higher; 2 studies, 209 participants; very low certainty of evidence). The reason for downgrading was imprecision due to the small number of participants and a high risk of bias.

Ventilator associated pneumonia (VAP)

One study reported VAP for 61 participants (Fig. 6). We found that selective decontamination probably decreases the risk of VAP compared to placebo (RR 0.30, 95% CI 0.13–0.72; risk difference (RD) 373 fewer per 1000, 95% CI 464 fewer to 149 fewer; 1 study, 61 participants; very low certainty of evidence). The reason for downgrading was imprecision due to only one study, the small number of participants, and a high risk of bias.

We found no data regarding serious adverse events, adverse events, and quality of life.

Table 2 Summary of findings table comparing of Ampicillin & Penicillin vs. standard care

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Ampicillin & penicillin
All-cause mortality	47 (1 RCT)	⊕○○○ Very low ^{a, b}	RR 1.04 (0.57 to 1.92)	458 per 1.000	18 more per 1.000 (197 fewer to 422 more)

Table 3 Summary of findings table comparing of selective decontamination vs. placebo

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with selective decontamination
All-cause mortality	209 (2 RCTs)	⊕○○○ Very low ^{a, b, c}	RR 1.01 (0.55 to 1.85)	167 per 1.000	2 more per 1.000 (75 fewer to 142 more)
Duration of mechanical ventilation	209 (2 RCTs)	⊕○○○ Very low ^{a, c}	-	The mean duration of mechanical ventilation was 8.05 days	MD 1.22 days higher (1.41 lower to 384 higher)
ICU length of stay (ICU LoS)	148 (1 RCT)	⊕○○○ Very low ^{a, d}	-	The mean ICU length of stay was 15.7 days	MD 0.3 days higher (3.99 lower to 4.59 higher)
Ventilator associated pneumonia (VAP)	61 (1 RCT)	⊕○○○ Very low ^{a, d}	RR 0.30 (0.13 to 0.72)	533 per 1.000	373 fewer per 1.000 (464 fewer to 149 fewer)

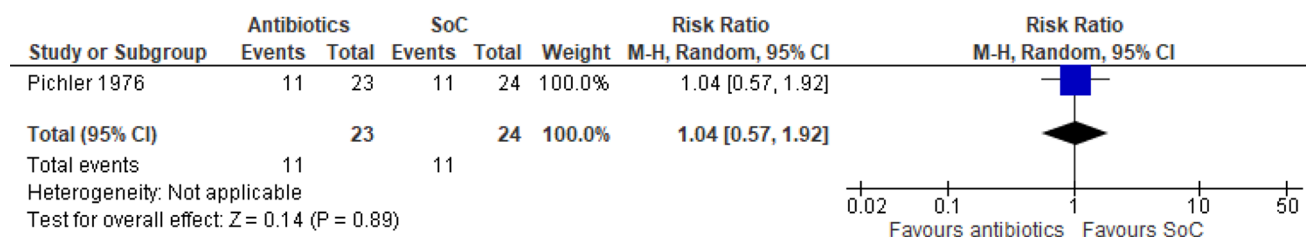
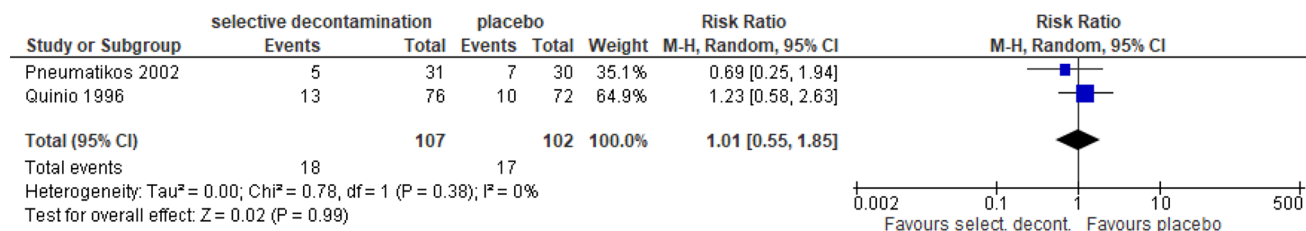
CI: confidence interval; MD: mean difference; RR: risk ratio

a. High risk of bias due to no pre-specified analysis plan, no information regarding concealment or blinding and no information regarding analysis method

b. Inconsistency due to inconsistent direction

c. Imprecision due to few patients

d. Imprecision due to few patients and only one study

**Fig. 2** Forest plot describing the difference between antibiotics compared to standard care regarding all-cause mortality**Fig. 3** Forest plot describing the difference between selective decontamination compared to placebo regarding all-cause mortality

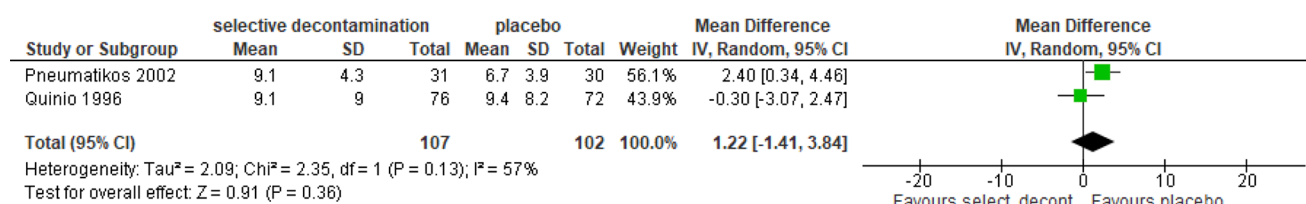


Fig. 4 Forest plot describing the difference between selective decontamination compared to placebo regarding duration of mechanical ventilation

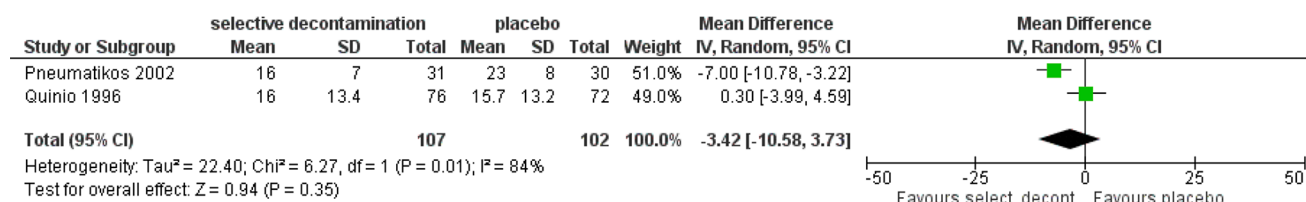


Fig. 5 Forest plot describing the difference between selective decontamination compared to placebo regarding ICU length of stay

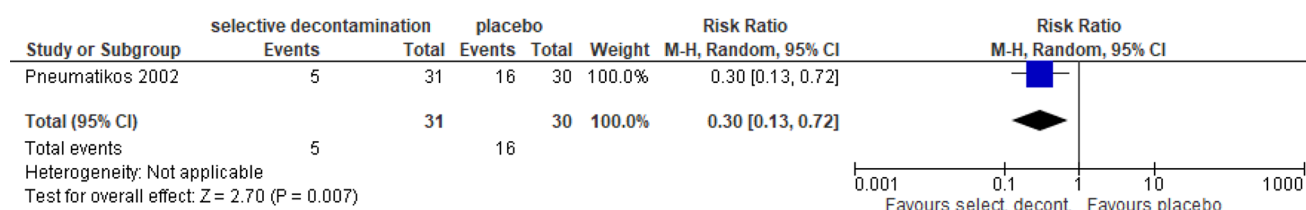


Fig. 6 Forest plot describing the difference between selective decontamination compared to placebo regarding VAP

Discussion

In this review, three RCTs comparing antibiotic prophylaxis with placebo or standard care in 256 adult polytrauma patients were included. The results indicate no significant differences in all-cause mortality, duration of mechanical ventilation, and ICU length of stay when comparing antibiotic prophylaxis to placebo or standard care. However, selective decontamination was associated with a reduction in the risk of VAP, highlighting its potential role in specific patient populations.

These findings align with those of prior systematic reviews, including Minozzi et al. [20], who demonstrated that topical prophylaxis reduces respiratory infections in mechanically ventilated patients, although mortality benefits were only observed with a combination of topical and systemic antibiotics. D'Amico et al. [8] reported benefits of combined antibiotic prophylaxis in reducing respiratory infections, but also regarding overall mortality, in critically ill patients. Nathens et al. [19] further emphasized that selective decontamination of the digestive tract reduces mortality in critically ill surgical patients, but not in medical patients, highlighting the variability of its effects across patient populations.

While the results of this review suggest that antibiotic prophylaxis has no significant effect on mortality or clinical outcomes in polytrauma patients, certain clinical scenarios

merit consideration. In particular, antibiotic prophylaxis may be beneficial in high-risk polytrauma patients requiring prolonged mechanical ventilation or immunosuppressants. The potential role of selective decontamination in reducing the risk of VAP is noteworthy, especially in settings where the prevalence of infections is high. However, these applications must be carefully weighed against the risks of antibiotic resistance and adverse effects. Tailored approaches based on local epidemiological data and individual patient profiles may optimize the use of antibiotic prophylaxis.

Despite these considerations, this systematic review has several limitations. The scarcity of high-quality RCTs, with one study dating back nearly 50 years, raises concerns regarding the applicability of these findings to contemporary clinical settings. Furthermore, the very low certainty of evidence, due to a high risk of bias among the studies and the small number of participants, weakens the strength of the conclusions. These limitations significantly restrict the applicability of these findings to contemporary clinical settings.

Given these limitations, this systematic review highlights the urgent need for more robust, high-quality RCTs to provide more robust evidence. Future research should explore variations in antibiotic prophylaxis approaches, patient subgroups, and contemporary clinical practices to better inform decision making. While this review provides a comprehensive synthesis of the available evidence, it underscores the

importance of cautious interpretation and the need for further studies to guide clinical practice. As the body of evidence evolves, clinicians must balance the potential benefits of antibiotic prophylaxis against its associated risks and individual patient needs to adapt guidelines based on the emerging evidence.

Conclusion

The results indicate that antibiotic prophylaxis has no significant effect on mortality and clinical status compared with placebo or standard care in adult polytrauma patients but may reduce the risk of VAP. However, the evidence is outdated and of very low certainty, with insufficient data to draw definitive conclusions regarding efficacy. Therefore, high-quality, up-to-date research is urgently needed to support clinical decision-making, and current interpretations should be treated with caution.

Appendix no 1. Search strategy

Search section: Evidence Syntheses.

1. PubMed.

#1 "Multiple Trauma"[mh] OR "Trauma Centers"[mh] OR polytrauma*[tw] OR "multiple trauma*"[tw] OR "major trauma*"[tw] OR "multiple injur*"[tw] OR "multisystem trauma"[tw] OR "multi-system trauma"[tw] OR "multisystem injur*"[tw] OR "multi-system injur*"[tw] OR "multitrauma"[tw] OR "multi-trauma"[tw] OR "life-threatening trauma*"[tw] OR "trauma patient*"[tw] OR "trauma population*"[tw] OR "trauma care"[tw] OR "trauma team*"[tw] OR "trauma cent*"[tw] OR "trauma unit*"[tw] OR "trauma resuscitation unit*"[tw] OR "Critical Illness"[mh] OR "Critical Care"[mh: noexp] OR "critical illness*"[tw] OR "critical care"[tw] OR "intensive care"[tw] OR "critically ill"[tw] OR "acutely ill"[tw] OR (blunt[tiab] AND trauma[tiab])

(379'990)

#2.

"Antibiotic Prophylaxis"[mh] OR (("Anti-Bacterial Agents"[mh]) AND ("Wound Infection/prevention and control"[mh] OR "Sepsis/prevention and control"[mh])) OR "antibiotic prophylaxis"[Title/Abstract:~3] OR "antibiotics prophylaxis"[Title/Abstract:~3] OR "antibiotics prophylactic"[Title/Abstract:~3] OR "antibiotic prophylactic"[Title/Abstract:~3] OR "antibacterial prophylaxis"[Title/Abstract:~3] OR "anti-bacterial prophylaxis"[Title/Abstract:~3] OR "prophylactic antibacterial"[Title/Abstract:~3] OR "prophylactic anti-bacterial"[Title/Abstract:~3] OR

"antibiotic premedication"[Title/Abstract:~3] OR "antibiotic premedications"[Title/Abstract:~3] OR "antibiotics premedication"[Title/Abstract:~3] OR "antibacterial premedication"[Title/Abstract:~3] OR "antibacterial premedications"[Title/Abstract:~3] OR "anti-bacterial premedication"[Title/Abstract:~3] OR "anti-bacterial premedications"[Title/Abstract:~3] OR "sepsis prevention"[Title/Abstract:~3] OR "antibiotic stewardship"[tw].

(35'716)

#3.

systematic[sb].

#4.

#1 AND #2 AND #3.

(78)

Search section: RCTs.

#5.

[Cochrane RCT-filter, sensitivity max. version] [21] (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])

#1 AND #2 AND #5.

(953)

2. Cochrane Central Register of controlled trials via Cochrane Library #1.

(polytrauma OR "multiple trauma*" OR "major trauma*" OR "multiple injur*" OR "multisystem trauma" OR "multi-system trauma" OR "multisystem injur*" OR "multi-system injur*" OR multitrauma OR multi-trauma OR "life-threatening trauma*" OR "trauma patient*" OR "trauma population*" OR "trauma care" OR "trauma team*" OR "trauma cent*" OR "trauma unit*" OR "trauma resuscitation unit*" OR "critical illness*" OR "critical care" OR "intensive care" OR "critically ill" OR "acutely ill"):TI, AB, KY.

#2.

((antibiotic* OR antibacterial OR anti-bacterial) NEAR/3 (prophylaxis OR prophylactic OR premedication*)):TI, AB, KY.

#3.

#1 AND #2 (206).

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Data availability Additional study data are available from the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

- in der Klinik für Operative Intensivmedizin und Intermediate Care des Universitätsklinikums Aachen

hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Karolina Dahms**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation: Dahms K., Mikolajewska A., Ansems K., Metzendorf M.-I., Benstoem C., Stegemann M.: Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis; European Journal of Medical Research; 2023, 28(1). geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

	K. Dahms	A. Mikolajewska	K. Ansems	M.-I. Metzendorf	C. Benstoem	M. Stegemann	Summe (%)
Studiendesign/ Konzeption	50	20			10	20	100
Tätigkeit des Informations-spezialisten				100			100
Kontrolle der Suchstrategie	100						100
Sichtung der Literatur	100						100
Sichtung der Literatur im 4-Augen-Prinzip		50	50				100
Datenextraktion	100						100
Kontrolle der Datenextraktion		50	50				100
Datenauswertung in RevMan	100						100
Kontrolle der Datenauswertung in RevMan		50	50				100
Bewertung des Verzerrungsrisikos sowie des Evidenzgrades	100						100
Kontrolle der Bewertung des Verzerrungsrisikos sowie des Evidenzgrades		40	30			30	100
Interpretation der Datenauswertung	100						100
Kontrolle der Interpretation der Datenauswertung		40	30			30	100
Verfassung des Manuskripts	100						100
Korrektur des Manuskripts	30	20	10	10	10	20	100
Finalisierung und Einreichung des Manuskripts	100						100
Sprachliche Optimierung (englische Sprache) mit Hilfe von ChatGPT	100						100

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Karolina Dahms**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation:

Dahms K., Ansems K., Dormann J., Steinfeld E., Janka H., Metzendorf M.-I., Breuer T., Benstoem C.: Effectiveness of antibiotic prophylaxis in polytrauma patients: a systematic review and meta-analysis; European Journal of Trauma and Emergency Surgery; 2025, 51(1). geleistet haben.

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	K. Dahms	K. Ansems	J. Dormann	E. Steinfeld	H. Janka	M.-I. Metzendorf	T. Breuer	C. Benstoem	Summe (%)
Studiendesign/ Konzeption	50					10	15	25	100
Tätigkeit des Informations-spezialisten					50	50			100
Kontrolle der Suchstrategie	100								100
Sichtung der Literatur	100								100
Sichtung der Literatur im 4-Augen-Prinzip		30	30	40					100
Datenextraktion	100								100
Kontrolle der Datenextraktion			50	50					100
Datenauswertung in RevMan	100								100
Kontrolle der Datenauswertung in RevMan			50	50					100
Bewertung des Verzerrungsrisikos sowie des Evidenzgrades	100								100
Kontrolle der Bewertung des Verzerrungsrisikos sowie des Evidenzgrades		50	50						100
Interpretation der Datenauswertung	100								100
Kontrolle der Interpretation der Datenauswertung							50	50	100
Verfassung des Manuskripts	100								100
Korrektur des Manuskripts	30	10	10	10	10	10	10	10	100
Finalisierung und Einreichung des Manuskripts	100								100
Sprachliche Optimierung (englische Sprache) mit Hilfe von ChatGPT	70						30		100

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

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Eschweiler, 16.04.2026