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REVIEW

Ethical publishing in intensive care medicine: A narrative review

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Abstract

Ethical standards in the context of scientific publications are increasingly gaining attention. A narrative review of the literature concerning publication ethics was conducted as found in PubMed, Google Scholar, relevant news articles, position papers, websites and other sources. The Committee on Publication Ethics has produced guidelines and schedules for the handling of problem situations that have been adopted by professional journals and publishers worldwide as guidelines to authors. The defined requirements go beyond the disclosure of conflicts of interest or the prior registration of clinical trials. Recommendations to authors, editors and publishers of journals and research institutions were formulated with regard to issues of authorship, double publications, plagiarism, and conflicts of interest, with special attention being paid to unethical research behavior and data falsification. This narrative review focusses on ethical publishing in intensive care medicine. As scientific misconduct with data falsification damage patients and society, especially if fraudulent studies are considered important or favor certain therapies and downplay their side effects, it is important to ensure that only studies are published that have been carried out with highest integrity according to predefined criteria. For that also the peer review process has to be conducted in accordance with the highest possible scientific standards and making use of available modern information technology. The review provides the current state of recommendations that are considered to be most relevant particularly in the field of intensive care medicine.

Key words: Peer review; Duplicate publication; Plagiarism; Scientific misconduct; Publication retractions; Boldt fraud; Fujii fraud

Core tip: Ethical standards in the context of scientific publications are increasingly gaining attention. Recommendations to authors, editors and publishers of journals and research institutions were formulated by The Committee on Publication Ethics with regard to

issues of authorship, double publications, plagiarism, and conflicts of interest, with special attention being paid to unethical research behavior and data falsification. As scientific misconduct with data falsification damage patients and society, it is important to ensure that only studies are published that have been carried out with highest integrity according to predefined criteria and that also the peer review process has to be conducted in accordance with the highest possible scientific standards.

Wiedermann CJ. Ethical publishing in intensive care medicine: A narrative review. *World J Crit Care Med* 2016; 5(3): 171-179 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/171.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.171

INTRODUCTION

Clinicians and researchers must be able to rely on the integrity and fair presentation of biomedical publications. They have, after all, a vested interest in it[1]. In recent years, the traditional relationship of trust between authors of publications of clinical studies, editors of medical journals, and their readers has come to falter because of numerous examples of open scientific misconduct[2-7]. Numerous journals in intensive care medicine have been affected by the increased number of published articles that they have had to retract. Measures to preserve scientific integrity are therefore becoming increasingly important. These include recommendations how to perform and present clinical studies. What publishers of scientific journals undertake to ensure the integrity of the scientific literature has become a recognized performance criterion[8]. The integrity of a biomedical journal depends on the ethical conduct of those who carry the greatest responsibility for the research publications, namely the authors, on the one hand, and the publishers, on the other, who need to understand that honest mistakes are inevitable, and are able to distinguish them from deliberate wrongdoing.

The editors need to ensure that all articles published in their journals fulfill the highest standards of scientific integrity[9]. Previously, when confronted with integrity problems, editors behaved as though unethical behavior of authors was not in their area of responsibility. Today, most of them have recognized that time and energy need to be invested in the investigation of allegations of scientific misconduct in order to ensure the scientific integrity of the journal. According to a recent survey of 200 leading journals, only two-thirds have fixed rules on withdrawal of publications, and in 95% they would be allowed to opt for such a move even against the will of the authors[10].

Usually, accusations of wrongdoing are raised by referees or readers. Publishers may and can assume that the whistleblower is acting in good faith and that their anonymity must be protected. Accused authors again must be considered as innocent until the suspected misconduct has undergone careful examination and proven to be such. The principles underlying such an investigative procedure are the subject of this review paper. In this context, collaboration between journals and research institutions is of key importance[11]. Based on the experiences of the recent past, the relevant issues include questions about misrepresentation of study designs, faulty statistics, double publications, data falsification, withdrawal of unreliable publications, and assessment of submitted manuscripts, including peer review, authorship issues and conflicts of interest. This review describes the principles of ethical publishing. It gives an overview on the subject. Statements are based on the available literature and the recommendations of the Committee on Publication Ethics (COPE) (http://publicationethics.org). The problems addressed relate to allegation or evidence of various types of reporting bias, plagiarism, double publications, multiple submissions, fragmented multiple publications of research findings of individual studies, and selective reporting; authorship; falsification and fabrication of data; and withdrawal of published articles.

METHODOLOGY

This narrative review has been made to address the problems of publication ethics in intensive care medicine. Author reviewed available literature, reports and surveys on the integrity of publications on critical care medicine as found in PubMed, Google Scholar, relevant news articles, position papers, websites and other sources.

UNETHICAL PUBLISHING IN INTENSIVE CARE MEDICINE

Retractions of publications are a sign that a journal takes seriously its responsibility for the integrity of its publications. Erroneous, unethical or fraudulent studies must be indicated to be such by using the possible formats "Expression of Concern", "Erratum", "Corrigendum" and "Notice of Retraction" or "Retraction Note" in order to ensure the scientific community that the publications in question have been assessed correctly and can be quickly identified as such in the literature databases.

Until a few years ago, relatively few retracted publications in the field of intensive care medicine were made public (Table 1). Recently, there has been an exponential growth in publication retractions both in biomedical literature and in the field of intensive care (Figure 1). This has as much to do with the capabilities of modern information technology and their impact on academic medicine and medical research as with changes in career opportunities for researchers and the

Table 1 Retracted publications arising from 28 critical care journals

Journal	Retractions (*n*)	Retracted Fujii papers (*n*)	Retracted Boldt papers (*n*)
American Journal of Critical Care	-	-	-
American Journal of Respiratory and Critical Care Medicine	7	-	-
Anaesthesia and Intensive Care	6	6	-
Anästhesiologie Intensivmedizin Notfallmedizin Schmerztherapie	6	-	6
Annals of Intensive Care	-	-	-
Burns	-	-	-
Chest	5	-	-
Critical Care	-	-	-
Critical Care and Resuscitation	-	-	-
Critical Care Clinics	-	-	-
Critical Care Medicine	5	-	2
Critical Care Nurse	-	-	-
Current Opinion in Critical Care	1	-	-
Injury	2	-	-
Intensive Care Medicine	7	-	6
Journal of Critical Care	-	-	-
Journal of Intensive Care Medicine	-	-	-
Journal of Neurotrauma	1	-	-
Journal of Trauma and Acute Care Surgery	-	-	-
Journal of Trauma Nursing	-	-	-
Medicina Intensiva	-	-	-
Minerva Anestesiologica	2	1	1
Neurocritical Care	-	-	-
Pediatric Critical Care Medicine	-	-	-
Respiratory Care	1	-	-
Resuscitation	3	-	-
Seminars in Respiratory and Critical Care Medicine	-	-	-
Shock	2	-	-
Total	48	7	15

Results of a PubMed search (available from: URL: http//www.ncbi.nlm.nih.gov/pubmed) on 05/04/2015. Search term "retraction of publication[publication type" and "american journal of critical care" (journal) or "american journal of respiratory and critical care medicine" (journal) or "anaesthesia and intensive care" (journal) or "anasthesiologie intensivmedizin notfallmedizin schmerztherapie" (journal) or "annals of intensive care" (journal) or "burns" (journal) or "chest" (journal) or "critical care" (journal) or "critical care and resuscitation" (journal) or "critical care clinics" (journal) or "critical care medicine" (journal) or "critical care nurse" (journal) or "current opinion in critical care" (journal) or "injury" (journal) or "intensive care medicine" (journal) or "journal of critical care (journal) or "journal of intensive care medicine" (journal) or "journal of neurotrauma" (journal) or "journal of trauma and acute care surgery" (journal) or "medicina intensiva" (journal) or "minerva anestesiologica" (journal) or "neurocritical care" (journal) or "pediatric critical care medicine" (journal) or "respiratory care" (journal) or "resuscitation" (journal) or "seminars in respiratory and critical care medicine" (journal) or "shock" (journal).

changing financial environment for research. And the number of publications retracted can be expected to rise in the future[12].

Two cases of research fraud in critical care medicine and anaesthesia

In the field of intensive care medicine, the majority of article withdrawals were made by leading international

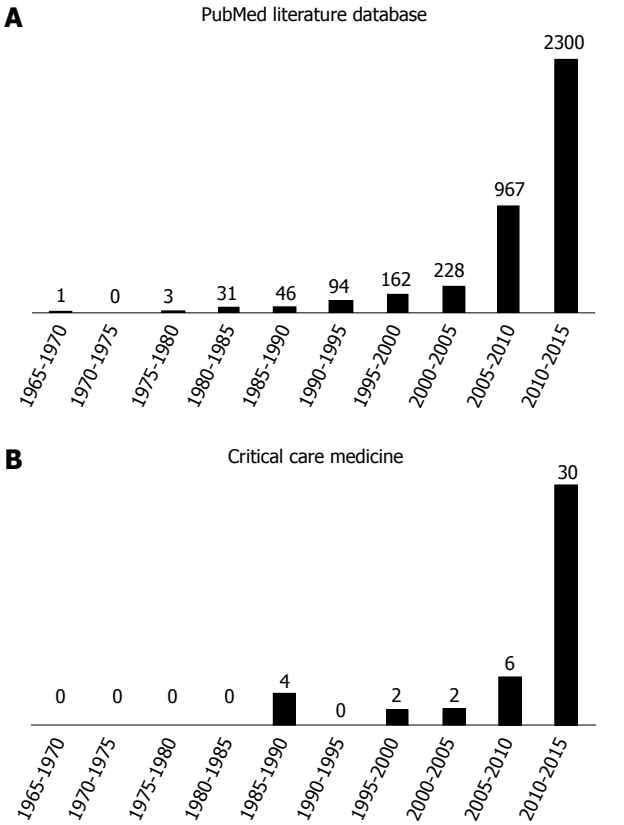

Figure 1 Retracted publications in biomedical literature and those arising from 28 critical care journals in the last five decades. Results of a PubMed search (available from: URL: http//www.ncbi.nlm.nih.gov/pubmed) on 05/04/2015 with the search term (A) "retraction of publication (publication type)" for the biomedical literature and (B) that of Table 1 for the critical care medicine literature (search terms described in Table 1).

scientific journals of the United States and Europe (*Am J Resp Crit Care Med*, *Chest*, *Crit Care Med*, *Intensive Care Med*). These are rather high-impact and not low-impact journals[13]. It is interesting to note that out of 28 involved journals, two national journals, namely "*Anaesthesia and Intensive Care*" and "*Anaesthesiology Intensive Care Emergency Medicine Pain Therapy*" from Australia and Germany, respectively are responsible for a quarter of all withdrawals in the field of intensive care (Table 1): All six articles retracted by "*Anesthesia and Intensive Care*" were articles of the Japanese author Fujii and all six withdrawals by the journal "*Anaesthesiology Intensive Care Emergency Medicine Pain Therapy*" were publications of Boldt in Germany. These two cases of scientific misconduct represent almost half (22/48) of all publication retractions in this area of medical research and therefore need further scrutiny. In seven of the 48 retracted articles in the area of intensive care, "*Intensive Care Medicine*" was involved and six of them were publications of Boldt. The exact scope of his fraud has neither been clearly determined, nor fully investigated. What is clear is that Joachim Boldt as an author of more than 215 publications on clinical trials had no authorization from the relevant ethics committees at both places where

Table 2 Cooperation between research institutions and journals on research integrity cases: Guidance from the committee on publication ethics

Who should	Do what
Institutions	Have a representative or an office for research integrity with highly visible contact details
	Inform magazines about cases of misconduct, in which the reliability of published data is doubtful
	Respond to journals when requested for information on issues such as disputed authorship, questionable data quality, existing conflict of interest or other issues that could affect the reliability of the published works, including honest errors
	Initiate investigations into allegations of scientific misconduct or unacceptable publication
	Have guidelines to support responsible research and provisions for implementation of investigative procedures in cases of suspected scientific misconduct
Journals	Give the contact details of the publisher responsible for questions of research and publication integrity
	Inform institutions if they suspect that wrongdoing by their researchers and submit evidence which support these concerns
	Cooperate with the institutions in question and in investigations suspected misconduct
	Be ready to announce retraction or correction of publications according to the guidelines on COPE if investigations confirm misconduct
	Have guidelines for responding to institutions and other organizations that investigate suspected cases of scientific misconduct

COPE: Committee on publication ethics (available from: URL: http//publicationethics.org/resources/guidelines).

he worked (University Hospital of Giessen and Klinikum Ludwigshafen) for carrying out research on patients. Therefore, a total of 88 of his publications were retracted in March 2011 for the time being.

The Fujii fraud: In 2000, a letter to the editor was published in "*Anesthesia and Analgesia*" that questioned the credibility of information on adverse drug reactions, because they were almost always identical in the 47 articles of the Japanese author Dr. Yoshitaka Fujii[2]. Against this background of suspicion of falsifying data, many years later, when the author submitted a manuscript to another journal, the matter was thoroughly investigated in cooperation with the publisher and the author's research institution with the result that it was found that no ethics committee approval had been obtained for the study, and furthermore, data manipulation was detected[3]. At the same time, the British anesthesiologist Dr. John Carlisle checked the integrity of the data of a total of 168 randomized controlled trials that Dr. Fujii had published over the years. He gave overwhelming statistical evidence that it was highly unlikely that the statistical distributions of continuous and categorical variables described in the publications are what could be expected to occur by chance[4]. After further examination of several Japanese universities where Dr. Fujii had worked continuously only for a few years each, the suspicion of falsification could not be discounted. Finally, a hitherto unprecedented number of 189 publications in anesthesia and intensive care medicine journals were recommended for retraction by the Japanese Society for Anesthesia.

In the case of the Japanese anesthesiologist Dr. Yoshitaka Fujii, who had worked in six Japanese universities and falsified a large number of publications, the involved academic institutions, in collaboration with the Japanese Society of Anesthesiology, quickly analyzed 300 articles after a group of editors and researchers suspected fundamental problems in many of his publications[2-4].

Although the fraudulent publications were discovered to be such only years later, recommendations to have these retracted were made to the responsible editors in a relatively short time, because the involved Japanese institutions and journals worked together constructively. Although research scandals are rated negatively by the public, in the end, particularly research institutions can benefit from this kind lively professionalism.

The Boldt fraud: In announcing the retraction of an article by Dr. Joachim Boldt, a group of editors declared that lack of ethics committee approval of a study does "not (...) mean that the research results per se are fraudulent"[5]. Data fraud was found in 10 of the publications[14]. The Klinikum Ludwigshafen could not find study documents on 92% of patients recruited for studies[14]. Suspicious homogeneity in the mortality data was seen in five publications[15]. Six publications on cardiac and major abdominal surgery showed suspiciously low interleukin-6 measurement variability[16-21]. For two of the six articles[17,19] data for comparative analysis were available in a thesis[22]. The dissertation showed that the articles misrepresented a single study as two separate studies, and that data had been manipulated to conceal the double publication.

Dissertations as a data source for fraudulent publications were found in two other retractions, one of which had already been withdrawn due to lack of ethics committee approval[23-25]. As of today, 89 publications have been retracted because they had failed to obtain ethics committee approval[5]; there are additional articles that have been retracted because of data falsification and double publications: two because of proven fabrication of data[26,27], and two because of proven data manipulation[28,29].

In 2012, the Klinikum Ludwigshafen pointed out that only those publications of Dr. Boldt had been examined that had appeared after 1999[14]. Because nearly 40% of clinical trials were carried out at the University Hospital Giessen, and articles based on these trials were published prior to 1999 and because thesis data were

falsified in publications[17,19,22-25], it can be assumed that falsification occurred prior to 1999.

In the meantime, comparative analysis of theses and publications are being carried out at the University of Giessen. Initial results have led to a series of further retractions, all of which are explained by systematic data falsification and partly with simultaneous dual publication[30-33] and trial design change[34]. From a confidential communication from the University of Giessen to the editors of the journals involved, from which "Retraction Watch"[35] was permitted to quote, it can be assumed that there are still large numbers of other publications of clinical studies of Boldt that will be retracted because of scientific misconduct going beyond lack of approval from ethics committee[34]. Among the most important issues that arise from the fraudulent series of Boldt is: How was it possible for Boldt to publish over a period of 25 years, working at two research facilities only, at least 217 articles on clinical trials involving thousands of patients with more than 180 co-authors (Christian J Wiedermann, unpublished survey) without arousing any suspicion of misconduct in institutions where he worked and the co-authors?

CORRECTING UNETHICAL LITERATURE

Research-based institutions as well as scientific journals are obliged to fulfill their different responsibilities. Institutions are responsible for the conduct of research and the promotion of a healthy research environment. Journals are responsible for assuring that their editors uphold the high scientific quality of all their publications. On issues of integrity of the research, it is important for both sides to communicate and to cooperate with each other effectively. To achieve this, COPE has issued recommendations[36], according to which the obligations are defined (Table 2).

Data falsification, plagiarism, double publications and irregularities in the authorship are the most common reasons for journal editors for having to deal with the question whether published articles should be retracted. Other problems are those of patients' rights and whether they were taken into consideration and whether permission was obtained from ethics committees. The retraction of publications should not be confused with "errata" or "corrigenda" - these are necessary when journals make some mistakes during production or when authors seek to retrospectively correct honest mistakes.

Identification of plagiarism and data falsification

With word processors, it has become easy to copy data and texts when writing scientific articles and exchange texts between documents and thus inadvertently or intentionally produce plagiarized texts. It is therefore important that citations and paraphrasing are properly done. It must be clear that the copying of existing documents is only permitted if the copied sections are clearly labeled as such, for example, by the text being enclosed in quotation marks and by correctly specifying the sources. Many institutions and scientific journal, particularly in English-speaking countries, now check submitted texts with commercial plagiarism software. One such text-comparative software is "iThenticate", which, in conjunction with a large database of published scientific documents called "Crosscheck" provided by publishers, detects plagiarism and redundant publication. One disadvantage of these systems is that analysis is limited to determining the number of copied words, and the number of copied words that is acceptable is defined by the institutions themselves and the journals[37]. Another disadvantage is that figures cannot be compared. The publishers of journals must themselves specify their evaluation criteria for text and picture similarities.

In surveys made, on average 2% of scientists admitted to having falsified research data at least once, and up to 34% admitted to having used other questionable research practices[38]. The actual frequency is likely to be even higher.

The approach to statistically identify potentially fraudulent data in publications of randomized clinical trials (RCTs) was developed and refined by Carlisle *et al*[39] so that "improbability" in the distribution of data in RCTs can be determined with increasing accuracy. It is conceivable that, in the foreseeable future, such statistical methods will be introduced in the publication routine - analogous to the use of software for detection of plagiarism to check plausibility of data integrity[40], which should become possible at least for prolific authors.

Retraction

Retractions of unreliable publications are important for scientific but also for economic reasons. After an investigation for misconduct, retracted publications of research projects that were funded by the "National Institutes of Health" in the United States lost about $58 million in direct financing in 1992-2012, representing on average US$ 392.582 per article). Researchers affected by withdrawal of one of their articles suffered a 90% decline in their publication output and large losses in the further financing of their projects[41]. Coauthors are not privy enough in publications also suffer from being under suspicion of participation in falsification and often without their knowledge. Their interest in correct publication practice can be used in strategies against unethical publishing[42].

Editorial efforts necessary for retracting a fraudulent publication are often enormous. Not least, the public loss of confidence arising from the misconduct and retraction of publications causes harm to scientific research itself. Although retracted publications represent only a small percentage of the total literature[43,44], it can be assumed that the number of unreported cases of falsified research reports is much higher than

is currently known. Only a fraction of the cases of scientific misconduct is actually uncovered and made public[38,45]. Worse still, the results of the retracted article continue to be cited[46-48]. Only in a fifth of the cases of announced retraction of scientific publications is research or publication misconduct cited as a reason by the journals for the retraction; in two-fifths of the cases, merely loss of credibility of data or their interpretation is cited as a reason[48].

From the fact of a journal withdrawing an article, is it permitted to conclude that the reason for retraction was scientific misconduct on the part of the authors? There are demands that this should not be done since there are several reasons why journals retract an article. This, however, is not a justifiable demand because authors identified as having falsified their data in one publication appear as authors in numerous retracted publications and thus distort the interpretation of the situation. Thus, although numerous articles of the anesthesiologist Dr. Joachim Boldt were retracted only for lack of ethics committee approval, suspicions of falsification were not investigated[49,50]. This shows how important the involvement of universities and research institutions in the review of falsification suspicion is, mainly because they have the ability to prove fraudulent intent and scientific fraud. This is underlined by the recent observation that even if regulatory authorities such as the American "Food and Drug Administration" (FDA) detects significant deviations from good clinical practice in clinical trials, they are seldom reflected in the clinical literature, and this happens even when there was clear evidence of data manipulation and other forms of scientific fraud[51,52]. As an example of misconduct in publication ethics, the FDA study for approval of the infusion solution Voluven® in United Sates can also be cited in this context: The nephrotoxic potential of this drug was indeed reported to the authorities, but was not been included in the publication, and this situation continues to this day without any relevant note of caution related to selective outcome reporting being added[53]. Another example is the FIRST trial[54], where the trial design has been published beforehand, but the final publication was different from the stated parameters[55].

Erratum, corrigendum and expression-of-concern

COPE guidelines explain when articles should be retracted, when corrections should be made and when only the "expression of concern" might be more appropriately used. Decisions that editors of journals must make still remain difficult. Thus, an analysis of the response of individual journals to a recent series of unethical publications of the German anesthesiologist Dr. Joachim Boldt that would need to be retracted according to the research institutions involved shows that only a small percentage of these have been dealt according to the COPE criteria[56].

For the researchers themselves and for the public, withdrawal of publications and the reasons for it[44,57-59], are of increasing interest. Both the absolute and relative number of retracted articles has increased dramatically. To what extent this represents an increase of scientific misconduct is unclear because journals also have better ways to detect especially plagiarism and multiple publications. Undoubtedly, researchers are under great pressure to publish and be "cited"[60].

Editors and publishers have the important duty to draw the attention of readers to scientific misconduct when publications have proven to be unreliable. In times of the conventional printing and traditional library catalogs, it was difficult to make any necessary corrections and any retractions of publications known in such a way that they could be brought into relation with the original articles. Today, the electronic publishing and cataloging system has simplified this task enormously. Readers are referred to corrections or retractions of texts at the very beginning of their electronic search. In this respect, supplementary information is already added to the table of contents and the article itself. Corrections and retractions are built directly into the affected article in this way. CrossMark (http://www.crossref.org/crossmark/) provides additional opportunities for cross-reference to refer the reader to comments and modifications of scientific publications. Thus, publishers can meet their responsibilities, so that retracted publications do not continue to be cited.

In case serious misconduct is suspected, the investigation of which takes more time to complete than expected, editors can warn readers of potential problems with an individual article even before completion of the investigations. In such cases, the publication of an "expression of concern" is advised by COPE.

DEGREES OF SEVERITY OF FRAUDULENT PUBLICATIONS

Even when intentional fraud seems obvious, ethical problems in publication may not be intentional and may arise out of ignorance or carelessness. This must be considered while investigating scientific misconduct. In the transparent description of such investigations, scientific journals as well as research institutions must handle the issue appropriately in accordance with the severity of misconduct involved. When plagiarism is suspected, there are differences in responsibility between senior researchers and young scientists in manuscript preparation, which should be reflected in the response of the journal to the submitted article, as well as the disciplinary measures taken by the institutions. The COPE algorithms describe in as differentiated a way as possible, how the publisher can respond to different types of ethical publication problems. Of course, not all aspects could be anticipated and some had to be left open and left to the co-operation between publishers, publishing houses and research institutions. One such issue is how to react to an anonymous informant.

CONCLUSION

Steps that need to be carried out by journal editors when confronted with unethical publishing include notifying the affected authors and research institutions, and investigation of the incident and publishing a report on it. It is important to be vigilant in order to detect breaches of publication ethics whenever they take place.

All authors must adhere to the principles of ethical publishing and agree with and conform to the policy of the journal in this regard. The corresponding author has obtained the consent of all the listed co-authors for the submission and publication of all versions of the manuscript. This is confirmed by all authors. All of the authors make their email address available, over which they are kept informed about all the steps up to the final step of publication or rejection.

All individuals have been added to the group of authors that have made a significant independent contribution to the manuscript.

The submitted manuscript is original and not already published elsewhere, except as oral presentation or poster with an abstract of no more than one page. In addition, the integrity of submitted articles is assured by the obligatory peer review process using all possible information technology and statistical tools.

The data of the manuscript have been obtained according to modern ethical standards taking into consideration the guideline recommendations such as those of PRISMA and free of decidedly non-authorized texts or data copies from other sources. All contents derived from previously published sources, either their own or those of others, are properly cited. Should any of the above-mentioned conditions be unmet, the authors are obliged to notify the journal as soon as possible about it. Correct statistics are important.

Editors, authors and reviewers must follow the basic rules of ethical publishing when submitting articles for publication, do peer reviewing or when they identify potential integrity problems when reading the articles. Most published articles are free of unethical behavior. Articles that, despite careful review process, violate good publication ethics, must be identified, analyzed and corrected or, where appropriate, retracted. In the work-up of problem cases, the methods formulated in the recommendations of COPE (http://publicationethics.org/resources/guidelines) can be put into use. "*Intensive Care Medicine*" makes full use of these recommendations. Rapid and close cooperation between authors, research institutions, the publisher of the journal and the publishing house is of the highest importance. It is emphasized that the critical reader plays an important role in the identification of irregularities and possible violation of good publication ethics. While respecting the reader anonymity, all concerned are encouraged to report suspected misconduct to the publication editor of the magazine.

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BRIEF ARTICLE

Retrospective Study

Enteral nutrition administration in a surgical intensive care unit: Achieving goals with better strategies

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Author contributions: Wilson S, Madisi NY and Kohli-Seth R contributed equally to this work; Wilson S helped in the acquisition of the data; Wilson S, Madisi NY and Kohli-Seth R analyzed, interpreted the data and drafted the manuscript; Bassily-Marcus A, Manasia A and Oropello J provided analytical oversight, revised the manuscript and material support; Kohli-Seth R contributed to the conception and design of the study, supervised the study and provided administrative support; all authors have read and approved the final version to be published.

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Abstract

AIM: To evaluate the impact of an enteral feeding protocol on administration of nutrition to surgical intensive care unit (SICU) patients.

METHODS: A retrospective chart review was conducted on patients initiated on enteral nutrition (EN) support during their stay in a 14 bed SICU. Data collected over a seven-day period included date of tube feed initiation, rate initiated, subsequent hourly rates, volume provided daily, and the nature and length of interruptions. The six months prior to implementation of the feeding protocol (pre-intervention) and six months after implementation (post-intervention) were compared. One hundred and four patients met criteria for inclusion; 53 were pre-intervention and 51 post-intervention.

RESULTS: Of the 624 patients who received nutrition support during the review period, 104 met the criteria for inclusion in the study. Of the 104 patients who met criteria outlined for inclusion, 64 reached the calculated goal rate (pre = 28 and post = 36). The median time to achieve the goal rate was significantly shorter in the post-intervention phase (3 d *vs* 6 d; $P = 0.01$). The time to achieve the total recommended daily volume showed

a non-significant decline in the post-intervention phase (P = 0.24) and the overall volume administered daily was higher in the post-intervention phase (61.6% *vs* 53.5%; P = 0.07). While the overall interruptions data did not reach statistical significance, undocumented interruptions (interruptions for unknown reasons) were lower in the post-intervention phase (pre = 23/124, post = 9/96; P = 0.06).

CONCLUSION: A protocol delineating the initiation and advancement of EN support coupled with ongoing education can improve administration of nutrition to SICU patients.

Key words: Enteral nutrition; Surgical critical care; Protocol; Critical care; Nutrition support

Core tip: Surgical critical care patients are more prone to frequent feeding interruptions for unavoidable reasons. In this study we validated that implementation of a feeding protocol in a surgical intensive care unit (SICU) decreased time to achieve goal rate and increased the total volume administered daily, despite frequent interruptions. It also increased detailed documentation by unit staff of interruptions allowing us to identify a trend with regard to feeding interruptions to better understand which practices/procedures require further review. The median time to achieve the goal rate was significantly shorter in the post-intervention phase. The time to achieve the total recommended daily volume showed a non-significant decline in the post-intervention phase and the overall volume administered daily was higher in the post-intervention phase. While the overall interruptions data did not reach statistical significance, undocumented interruptions (interruptions for unknown reasons) were lower in the post-intervention phase. To our knowledge, we are the second largest single center study supporting the benefit of implementing a feeding protocol in a SICU.

Wilson S, Madisi NY, Bassily-Marcus A, Manasia A, Oropello J, Kohli-Seth R. Enteral nutrition administration in a surgical intensive care unit: Achieving goals with better strategies. *World J Crit Care Med* 2016; 5(3): 180-186 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/180.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.180

INTRODUCTION

Nutrition support is an important element of managing surgical critical care patients. Perioperative malnourishment and prolonged catabolism can lead to multiple deleterious effects, including delayed or abnormal wound healing, secondary infections, muscle atrophy, and increased length of stay[1,2]. Providing early enteral nutrition (EN) helps meet the metabolic demands during the acute phase of surgery-associated critical illness, rebuilds nutritional stores during recovery, and reduces hospital mortality[3-6]. When oral feeding is not possible it is more physiologic to deliver nutrients through the gut to preserve its barrier role. EN is therefore preferred over parenteral nutrition (PN) as it has been shown to maintain gastrointestinal (GI) integrity and function and improve blood flow and peristalsis. It also prevents bacterial translocation, thereby decreasing the risk for systemic infections[7]. Existing literature shows that surgical patients are less likely to receive EN and more likely to receive PN compared to medical patients. Tube feeding is often delayed and patients are less likely to achieve nutritional adequacy following both elective and urgent surgery[8]. Patients undergoing gastrointestinal and cardiovascular surgeries receive the least amount of EN with no clear explanation[8]. Despite the known benefits, providing adequate nutrition early is challenging in the surgical intensive care unit (SICU) setting due to frequent interruptions from the scheduling of procedures and tests, perceived intolerance of tube feeding, ventilator weaning trials and routine nursing care. These lengthy and sometimes unnecessary interruptions lead to the inadequate administration of nutrition. Additionally, specific guidelines for controversial practices like checking gastric residual volume (GRV) can also lead to frequent and prolonged interruptions in feeding. Current literature on routine monitoring of GRV refutes the correlation between GRV and a patient's risk for ventilator associated pneumonia, ICU-acquired infections, mechanical ventilation duration, ICU length of stay, or mortality rates[9] however, complete abandonment of this long-standing practice remains a challenge. Given the obstacles to optimal EN support for SICU patients, it is evident that there is a need for more structured processes that guide practitioners and standardize practice.

MATERIALS AND METHODS

A quality improvement project was conducted in the SICU to determine whether patients were being adequately fed. Results indicated that 65% of patients did not achieve goal rate during the seven-day period, and 65% of patients received less than half of the total volume recommended daily. The results of this quality review coupled with the frequency and duration of tube feed interruptions led to the development of an EN feeding protocol. The protocol outlined instructions for more timely advancement of tube feeding to goal rate and incorporated guidelines intended to decrease unnecessary feeding interruptions.

The aim of this study was to evaluate whether the EN feeding protocol improved the ability to meet nutritional goals in a timely fashion and increased overall administration of nutrition during SICU stay.

Patients and settings

This study was conducted in the SICU of a 1171-bed

Table 1 Exclusion criteria

Exclusion criteria	*n*	Pre-intervention phase	Post-intervention phase
Enteral nutrition not initiated	10	8	2
Intestinal transplant	1	1	0
Tube fed < 48 h	30	13	17
Tube feed initiated before ICU admission	1	1	0
Patient to or for GI surgery	2	2	0
Not tolerating	1	1	0
Withdrawal of care	0	0	0
Total	45	26	19

Exclusion criteria with counts for pre-intervention, post-intervention and the total number of patients who met each criterion. ICU: Intensive care unit; GI: Gastrointestinal.

tertiary care teaching hospital. The SICU is a closed 14-bed unit that admits approximately 900 patients annually with an average length of stay of five days. Most SICU patients are post-operative from a variety of surgical specialties, including general surgery, surgical oncology, and liver and intestinal transplant. The charts of 624 adult patients over 18 years of age who received EN support for a one-year period were screened for inclusion in the study. Due to the retrospective nature of this study, the Institutional Review Board waived consent.

The pre-intervention phase was defined as the six months before the EN feeding protocol implementation and the post-intervention phase was the six months post implementation (Table 1).

The primary hospital admission date, SICU admission date, formula name, date of initiation, rate initiated, subsequent hourly rates, and volume provided daily were recorded over a seven-day period. The nature and length of interruptions were noted for all patients included in the study.

Intervention

The EN protocol delineated steps for initiating, advancing and maintaining nutrition support in these patients. Following implementation of the protocol, EN was started at half the goal rate. Gastric residual volumes were checked 6 h after initiation. If GRV were less than 250 mL, EN feeds were advanced to goal rate with GRV and signs and symptoms of intolerance monitored every 6 h, for the first 24 h, or until confirmation of tolerance of tube feeding at the goal rate. In the event that GRV was more than 250 mL, the bedside nurse would inform the physician on call for further assessment of symptoms such as abdominal pain, distention, tenderness, vomiting or high GRV ($\geqslant$ 500 mL). In the presence of any of these symptoms, EN feeding was held for 3 h with reevaluation thereafter. With implementation of the protocol, if symptoms were absent, the ICU team could start promotility agents, if not otherwise contraindicated. Promotility agents used included metoclopramide and erythromycin. The GRV was then rechecked after six hours and feeds advanced as indicated above. If EN was held due to intolerance or inability to advance to goal rate, PN support was considered. Stop rules for procedures were also developed to guide practitioners on the appropriate timing for holding EN support. For emergent procedures feeds would be held and NGT placed to suction to decompress the stomach. For non-emergent procedures, including planned surgery and elective tracheostomy, holding feeds 6 to 8 h prior to procedure was suggested, and for pressure support or weaning trials, holding feeds one hour prior to trial was advised. It was recommended that feeds be restarted upon return from procedure; pending confirmation from the primary team or upon determination that extubation was not possible (Figure 1). Nurses and physicians were educated on the protocol. The importance of clear and accurate documentation, including reason and duration of feeding interruptions was emphasized.

Statistical analysis

The Kaplan-Meier method was used to calculate the time to achieve goal rate and total recommended daily volume over the seven-day period. The Log-Rank test was used to compare the time to both of those events between the pre- and post-intervention phases. An aggregated average percent goal was calculated for each patient and compared. In addition, the percentage of patients who reached goal rate by day seven was compared. Interruptions were categorized by type into avoidable and unavoidable. Gastrointestinal surgeries, interventional radiology (procedures, access), tracheostomy/PEG tube placement, extubation/re-intubation, ventilator weaning trials, high GRV (> 500 mL), and abdominal imaging were considered unavoidable causes. Avoidable interruptions included imaging studies where the radiologist did not request fasting and GRV < 500 mL. The average length of interruptions by type in the pre- and post-intervention phases were also calculated and compared. The Statistical methods of this study were reviewed by John Doucette, Associate professor, preventive medicine at Icahn School of Medicine at Mt Sinai, New York.

RESULTS

Of the 624 patients who had nutrition support during the review period, 104 met criteria for inclusion in the study. Of the 104 who met criteria, 53 were pre- and 51 were post-intervention (Table 2).

The largest admitting service was GI surgery followed by transplant, vascular surgery, surgical oncology, orthopedics and medicine.

Of the 104 patients monitored during the seven-day period, 40 did not reach goal rate (pre = 25, post = 15). Among those who did not reach goal rate, 22 stopped enteral feeding before the seventh day due to extubation, transfer from ICU or hemodynamic instability (pre = 16/25, post = 6/15; P = 0.14). The remaining 18 patients continued on tube feeds for

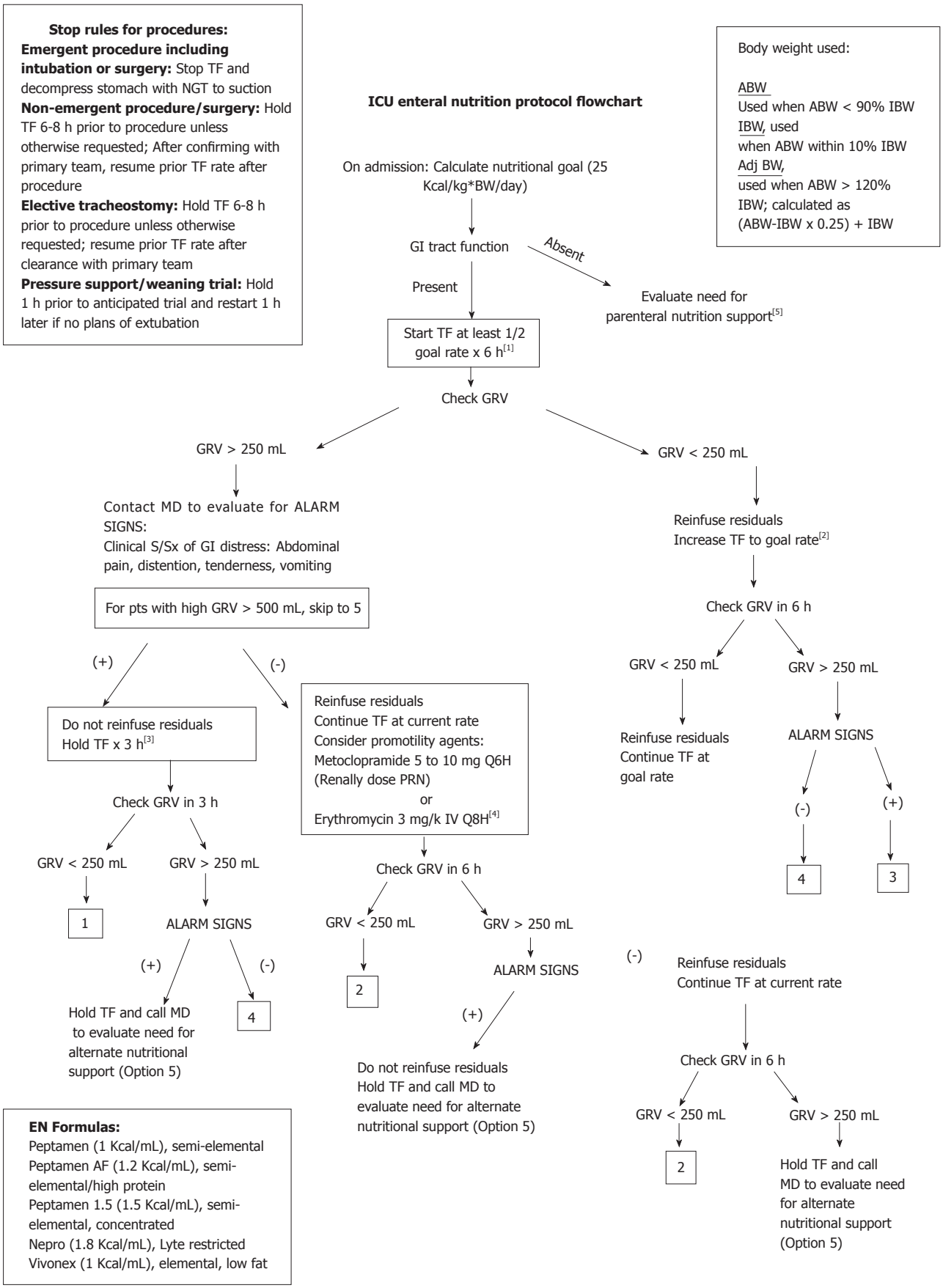

Figure 1 Intensive care unit enteral nutrition protocol flowchart. TF: Tube feeds; NGT: Nasogastric tube; GI: Gastrointestinal; PN: Parenteral nutrition; S/Sx: Symptoms and signs; pts: Patients; GRV: Gastric residual volume; ABW: Actual body weight; IBW: Ideal body weight; Adj BW: Adjusted body weight.

Table 2 Baseline characteristics and study cohort

Patient demographics	Pre-intervention phase	Post-intervention phase	All patients
Age (yr)	67 ± 16	66 ± 16	67 ± 16
Male	31 (58%)	26 (51%)	57 (55%)
Height (cm)	166.79 ± 11.59	167.09 ± 12.37	166.93 ± 11.91
Weight (kg)	76.7 ± 22.8	81.7 ± 25.5	79.1 ± 24.2
GI surgery	18 (34%)	27 (53%)	45 (43%)
Vascular surgery	8 (15%)	3 (6%)	11 (11%)
Transplant	14 (26%)	11 (22%)	25 (24%)
Medicine	3 (6%)	5 (9%)	8 (7.5%)
Surgical oncology	7 (13%)	1 (2%)	8 (7.5%)
Other (ENT, HIV medicine, orthopedics, orthopedic surgery, oral and maxillofacial surgery)	3 (6%)	4 (8%)	7 (7%)
Total	53	51	104

Data are reported as mean ± SD or *n* (%). Patient demographics (average age, gender, average height and average admission weight) and primary service caring for patient upon admission to ICU. ICU: Intensive care unit; GI: Gastrointestinal; HIV: Human immunodeficiency virus.

Table 3 Hold time (hours) median hold time and interquartile ranges by interruption type

Interruption	Pre-intervention phase	Post-intervention phase
Procedures	17.4 (9-19)	20 (7-24)
Residuals	17.5 (7-22)	21.5 (4-29)
Weaning	13.6 (4-15)	12.6 (7-14)
Other[1]	22.9 (10-48)	11.3 (3-15)
Undocumented	5.7 (3-4)	6.9 (4-10)
All interruptions	14.6 (4-17.25)	16.6 (5-22.5)

Data are reported as median and interquartile range. Length of interruptions by type during the pre- and post-intervention phases. [1]Nursing care, change in status, *etc*.

seven days without reaching goal rate.

The distribution of patients who reached goal rate was 55% (28/53) during the pre-intervention phase, and 71% (36/51) during the post-intervention phase. The median time to achieve goal was significantly shorter in the post-intervention phase (3 d *vs* 6 d; *P* = 0.01) (Figure 2). The overall time to achieve total recommended daily volume showed a non-significant decline in the post-intervention phase (*P* = 0.24) (Figure 3). The overall volume administered daily was higher in the post-intervention phase (61.6% *vs* 53.5%; *P* = 0.07).

There were 124 instances of TF interruptions in the pre-intervention phase and 96 in the post-intervention phase. The most common reason was tests and procedures (pre = 42/124, post = 49/96) followed by ventilator weaning (pre= 31/124, post = 19/96), GRV (pre = 22/124, post = 10/96), and "other" (which included nursing care, change in status and other miscellaneous reasons) (pre = 6/124, post = 9/96). Interruptions were categorized as "undocumented"

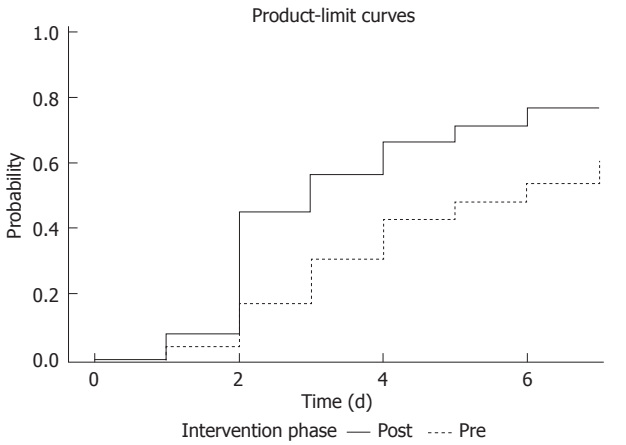

Figure 2 Days to achieve goal rate by intervention phase. The Kaplan-Meier method was used to calculate the time to achieve goal rate over the seven-day period. The log-rank test was used to compare the time to both of those events between the pre- and post-intervention phases.

when the reason could not be found in either the flow sheets or medical record. The overall interruption data did not reach statistical significance. However, undocumented interruptions were lower in the post-intervention phase (pre = 23/124, post = 9/96; *P* = 0.06) (Table 3).

DISCUSSION

To our knowledge, our study is the second largest single center study supporting the benefit of the EN protocol in a SICU[10]. We compared the timeliness to achieve goal rate, the amount of EN received, frequency of nutrition interruptions, and accuracy of documentation in critically ill surgical patients before and after implementation of the EN protocol. Guidelines recommend initiating enteral feeds within 24-48 h of ICU admission, yet up to 50% of patients do not even receive EN during their ICU stay[11,12]. Furthermore, EN interruption occurs more frequently in SICUs than their counterparts for multiple unavoidable reasons, including surgical procedures and imaging studies. Hence, these patients are at higher risk of iatrogenic malnutrition[13,14]. There is an overall lack of consensus on the duration of time to hold EN in preparation for a procedure among various specialists, including anesthesiologists, surgeons and intensivists[15]. Physicians are often reluctant to start EN in hemodynamically unstable patients, despite the overwhelming data showing improved outcomes[16]. Establishing criteria for when to interrupt tube feeding, and more importantly, when to restart feeding, may improve overall administration of nutrition support[17]. After conducting the QI project on enteral feeding in our SICU, we determined that 65% of patients on EN support did not achieve goal rate by the seventh day of administration and received less than 50% of the daily-recommended volume. The literature on developing protocols for EN administration suggests that outlining criteria for the initiation and advancement

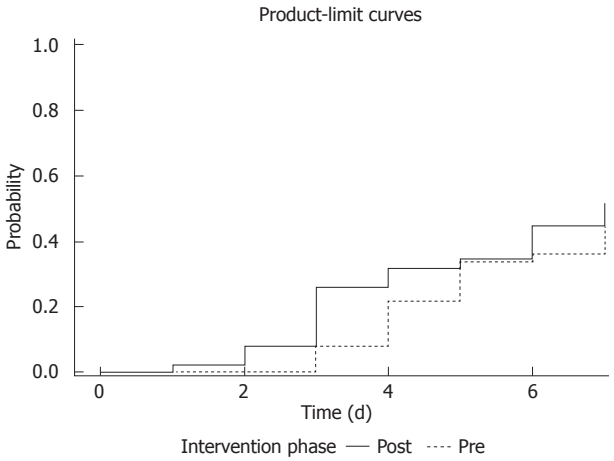

Figure 3 Days to achieve total recommended volume by intervention phase. The Kaplan-Meier method was used to calculate the time to achieve total recommended daily volume over the seven-day period. The log-rank test was used to compare the time to both of those events between the pre- and post-intervention phases.

of EN support may improve nutrient delivery[17,18]. Moreover protocols also serve as an effective tool for the physicians in-training, registered nurses and other support staff. Multiple protocols have been introduced over the past years in different aspects of critical care medicine (ventilator weaning, spontaneous breathing and awakening trails, sedation and analgesia) leading to better outcomes[19].

Despite prolonged hold times our data supports the use of an EN protocol to decrease time to achieve goal rate and increase the volume of tube feeding delivered daily. Though data on interruptions varied between the pre- and post-intervention phases, it highlighted the extensive duration of interruptions for various reasons. During the post-intervention phase one of the greatest challenges faced when executing the feeding protocol was overcoming existing nursing and physician practices regarding holding tube feeding and inconsistent documentation. Creating awareness among physician and nursing staff of enteral feeding practices led to an increase in accurate documentation.

Future research should focus on patient outcomes and quality indicators to promote the use of protocols for EN administration in the SICU, and further extended to other ICUs throughout the hospital. Optimizing the EN protocol by providing distinct instructions for how to minimize feeding interruptions could improve the parameters where significant progress was lacking between the pre and post intervention phases. Guidelines and strategies for moving the location of the tip of the feeding tube more distal in the jejunum could also assist in reducing length of hold times for feeding intolerance. Incorporating volume-based practices that summarize how to adjust tube-feeding rates in order to "catch-up" may also assist in optimizing the protocol, and increasing the overall administration of nutrition daily. By developing standards of practice and guidelines for when to hold and restart enteral feeds, we improved the overall administration of nutrition provided.

Given the retrospective nature of our study, we are unable to establish cause and effect. The study does not draw solid conclusions, however the data can be used to provide descriptive characteristics, and add to the limited literature available.

In conclusion, this study suggests a user friendly EN protocol in conjunction with extensive ongoing education may lead to shorter time to achieve goal rate, and enhance overall administration of nutrition to surgical critical care patients.

ACKNOWLEDGMENTS

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COMMENTS

Background

The benefits of enteral nutrition (EN) to critically ill patients are well cited in the reducing length of stay and hospital mortality. Clinical protocols serve as effective tools for guiding clinical practice and improving patient outcomes (*e.g.*, ventilator weaning, spontaneous breathing and awakening).

Research frontiers

EN is preferred over parenteral nutrition, as it has been shown to maintain gastrointestinal integrity and function, and increase peristalsis and blood flow. Discrepancies between prescribed nutrition goal and actual nutrition delivered in critically ill patients are not uncommon; this is especially the case in the surgical population. Prior studies have established that feeding protocols can increase administration of nutrition to patients. The current research hotspot is to implement a feeding protocol in a surgical intensive care unit (ICU) setting where the number of interruptions are frequent and goal rates are often not achieved.

Innovations and breakthroughs

Few studies to date have been conducted on the use of feeding protocols in surgical ICU patients. Existing literature suggests patients are less likely to get EN compared to medical ICU patients due to concern of postoperative ileus, anastomotic leak, diagnostic testing and operative procedures. To our knowledge, this study is the second largest single center study supporting the benefit of implementing a feeding protocol in surgical ICU. The feeding protocol was introduced and data collected on the rate initiated and total volume provided daily. The authors monitored time to achieve goal rate and the total volume provided six months prior to and following implementation of the protocol. Overall time to achieve goal rate decreased, while the total volume administered daily increased. The protocol also led to an increase in detailed documentation of interruptions by the unit staff.

Applications

The study results suggest feeding protocols can lead to improved nutrient administration during the acute phase. Improved documentation may allow them to identify and trend with regard to feeding interruptions to better understand which practices or procedures require further review.

Terminology

EN is any method of feeding that utilizes the gastrointestinal tract to deliver nutrients. Parenteral nutrition, also referred to as intravenous feeding, is a method of providing nutrition into the body *via* the veins.

Peer-review

This is a well-written paper, focused on an interesting topic.

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SYSTEMATIC REVIEWS

Predictive value of cytokines for developing complications after polytrauma

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Author contributions: This study represents a great deal of effort, resources and dedication on the part of the authors in reviewing the literature and performing statistical analyses; all authors have participated in a material way to at least three of the following elements: Study design, gathered data, analysed data, initial draft, ensured accuracy of data; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The technical appendix including the full search strategy for this systematic review is available from the corresponding author at A.E.Dekker@lumc.nl. Since this study did not involve any biostatistics, no statistical code and dataset are available.

Manuscript source: Invited manuscript

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Abstract

AIM: To investigate posttraumatic cytokine alterations and their value for predicting complications and mortality in polytraumatized patients.

METHODS: Studies on the use of specific cytokines to predict the development of complications and mortality were identified in MEDLINE, EMBASE, Web of Science and the Cochrane Library. Of included studies, relevant data were extracted and study quality was scored.

RESULTS: Forty-two studies published between 1988 and 2015 were identified, including 28 cohort studies and 14 "nested" case-control studies. Most studies investigated the cytokines interleukin (IL)-6, IL-8, IL-10 and tumor necrosis factor (TNF-α). IL-6 seems related to muliorgan dysfunction syndrome, multiorgan failure (MOF) and mortality; IL-8 appears altered in acute respiratory distress syndrome, MOF and mortality; IL-10 alterations seem to precede sepsis and MOF; and TNF-α seems related to MOF.

CONCLUSION: Cytokine secretion patterns appear to be different for patients developing complications when compared to patients with uneventful posttraumatic course. More research is needed to strengthen the evidence for clinical relevance of these cytokines.

Key words: Multiple trauma; Cytokine; Acute respiratory distress syndrome; Sepsis; Muli-organ dysfunction syndrome; Multi-organ failure

Core tip: Early identification of patients at risk for

developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and multiorgan failure. This article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death.

Dekker ABE, Krijnen P, Schipper IB. Predictive value of cytokines for developing complications after polytrauma. *World J Crit Care Med* 2016; 5(3): 187-200 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/187.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.187

INTRODUCTION

The term polytrauma is used to describe a combination of serious injuries in at least two different anatomical regions. Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Trauma initiates a local pro-inflammatory response, encompassing the activation of effector cells, complement cascade, coagulation system, cytokines, acute phase proteins and neuroendocrine mediators[1,2]. This sequence of events is part of the physiologic response to trauma, as it serves to initiate the healing process, prevents the host from additional injury and acts as a barrier against infection[3]. Yet extensive trauma can arouse a comprehensive systemic inflammatory state known as the systemic inflammatory response syndrome (SIRS). An overactivated pro-inflammatory reaction leads to progressive sequestration of leukocytes in vital organs, predisposing patients to the development of organ failure. In an attempt to mediate these deleterious effects, immunesuppressive mediators are released. This counter regulatory response syndrome (CARS) becomes active almost immediately after the onset of SIRS[4]. Despite dampening inflammation, CARS itself may have unfavorable effects as well, as it can induce an increased susceptibility to infections and sepsis[2]. The posttraumatic immunologic alterations of combined SIRS and CARS have been termed CHAOS (cardiovascular shock, homeostasis, apoptosis, organ dysfunctions and immune suppression)[5]. With an overwhelming initial traumatic insult, an overstimulated SIRS response initiates the chaos that results in early multiorgan failure (MOF), present within 72 h after injury[2,6]. A less severe initial insult may prime immune cells while eliciting a moderate inflammatory reaction. In this setting, a second insult ("hit") may strengthen the inflammatory reaction towards immune suppression, predisposing the patient to sepsis[7,8].

Cytokines play a pivotal role in both the pro-inflammatory and the anti-inflammatory reaction to trauma[9,10]. The pro-inflammatory cytokine interleukin-6 (IL-6) is secreted by a wide range of cells including neutrophils, T- and B-lymphocytes and endothelial cells[8,11]. Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β), and liberated after tissue damage and infection. The biologic activity of IL-6 includes increased T- and B-cell activation and proliferation, differentiation of cytotoxic T cells and enhanced activity of natural killer (NK) cells[12]. In addition, IL-6 mediates the induction of the acute phase response and reduces apoptosis in neutrophil granulocytes[4,11]. Combined actions lead to an effective SIRS response early after trauma. The pro-inflammatory cytokine IL-8 is an endogenous chemoattractant. Monocytes, macrophages, neutrophils and endothelial cells secrete IL-8, and its release is enhanced after stimulation with IL-1, TNF-α, C5a and LPS[9,13]. After activation, IL-8 induces expression of adhesion molecules on neutrophils and endothelial cells, which enables the migration of neutrophils to the site of production[4,9]. The anti-inflammatory cytokine IL-10 is primarily synthesized by CD4+ T_H2 lymphocytes and, to a lesser extent, by B lymphocytes, monocytes and macrophages[8]. Activated IL-10 decreases the cytokine production of T_H1 cells, reduces antigen presentation of macrophages and subsequent proliferation of T-lymphocytes, and suppresses monocyte function[4,14,15]. These actions make IL-10 one of the most important mediators in the anti-inflammatory immune response. The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma. The cytokine is produced by monocytes, macrophages, lymphocytes and T lymphocytes. After secretion, TNF-α increases endothelial cell permeability and adhesion properties, and activates macrophages, NK cells and lymphocytes. TNF-α also induces the secretion of various cytokines [IL-6, -8, -10, interferon (IFN-γ)] and immunoglobulin production[7,12]. Release of excessive TNF-α ultimately leads to accumulation of leukocytes in the injured tissues. Many of these cytokines attributed to the potential development of complications in polytrauma patient. Their exact causal role has not been detected yet.

Early identification of patients at risk for developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and MOF. Previous studies have acknowledged the correlation between markers of inflammation and clinical condition after polytrauma. The aim of the current review was: (1) to summarize the available

knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome (ARDS), sepsis, multiorgan dysfunction syndrome (MODS), MOF and mortality.

MATERIALS AND METHODS

The systematic review was performed in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[16]. Due to heterogeneity across the studies in terms of patient population, study design and analytical techniques used, and the small amount of studies for each biomarker-complication combination, a meta-analysis was not feasible.

Search strategy

Studies addressing the relation between complications after multiple trauma and cytokine concentrations, were identified in the following databases: MEDLINE (1988 - 18 January 2014), Embase (1988 - 18 January 2014), Web of Science (1988 - 18 January 2014) and the Cochrane Library (to Issue 1, 2014). The search strategy was developed by an information specialist, and carried out using various combinations of the key words "multiple trauma", "cytokines" and the complications "systemic inflammatory response sydrome (SIRS)", "ARDS", "sepsis", "MODS", "MOF" and "mortality". In addition, forward citation searches of selected studies and literature reviews were carried out. The initial search was not limited by language, publication date and type of publication. In February 2016, an additional literature search of the mentioned databases was carried out. One relevant new article was found.

Outcome definitions

Primary outcomes were the development of one or more of the following complications: (1) ARDS, determined in concordance with the American-European Consensus Conference 1994 definitions[17]; (2) sepsis, diagnosed when SIRS (defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992[18]) occurred in combination with a septic focus or positive blood culture; (3) MODS; and (4) MOF, in the included studies diagnosed based on different scoring systems[19-24]. The secondary outcome was mortality during a predetermined follow-up period of individual studies.

Study selection

Studies were scanned for eligibility based on title and abstract. Subsequently, eligibility of selected studies was assessed by retrieving the full text of the article. Inclusion criteria were prospective or retrospective cohort, case-control and cross-sectional studies including at least 10 adult multiple trauma patients (ISS $\geqslant$ 16). Excluded were articles in other language than English or German, animal studies and *ex vivo* studies, studies involving pediatric populations, case reports, review articles and letters/editorials. Studies not elaborating on the primary or secondary outcomes investigated in this review were also excluded. In addition, studies measuring cytokine concentrations in samples other than serum (*e.g.*, wound exsudate, broncho-alveolar lavage fluid) were not eligible for inclusion, as local alterations in concentration may not reflect the systemic changes in the immune reaction.

Data extraction

The following data were extracted from included studies: Title, study design, date of publication, size of study population, patient demographics, incidence of complications and mortality, follow-up period, type of cytokines studied, mean cytokine concentrations measured at specific moments during follow-up, and cut-off points with sensitivity and specificity. Data were extracted from figures when raw data were not available. In the case of duplicate publications, the most relevant or informative article was chosen.

Quality assessment

The quality of included studies was critically evaluated with the strengthening the reporting of observational studies in epidemiology (STROBE) statement[25].

Biostatistics statement

In this review of the literature no biostatistical methods were used. For this reason, no biomedical statistician was involved for statistical review.

RESULTS

Identification of studies

After exclusion of duplicate studies, the literature search yielded 730 potentially relevant articles. One hundred and thirty-eight articles passed the first screening and were retrieved for closer examination. Of the retrieved articles, 40 were eligible for study inclusion. The full text of six potentially relevant studies could not be obtained, which were therefore excluded from the analysis. Seven citations were found assessing reference lists of the included studies. One relevant article was encountered in the additional search carried out in 2016. The study selection procedure is outlined in Figure 1.

Study characteristics

The 42 included articles consisted of 28 cohort studies[3,13,26-51] and 14 "nested" case-control studies[11,14,52-63]. Two studies were retrospective[14,52]; the other 40 studies were prospective in study design. Studies were published between 1988 and 2015, and together included 5756 patients. The development of ARDS in relation to cytokine levels was investigated in seven studies; sixteen studies determined cytokine concentrations in sepsis; MODS development was assessed in ten studies; and eleven studies reported cytokine

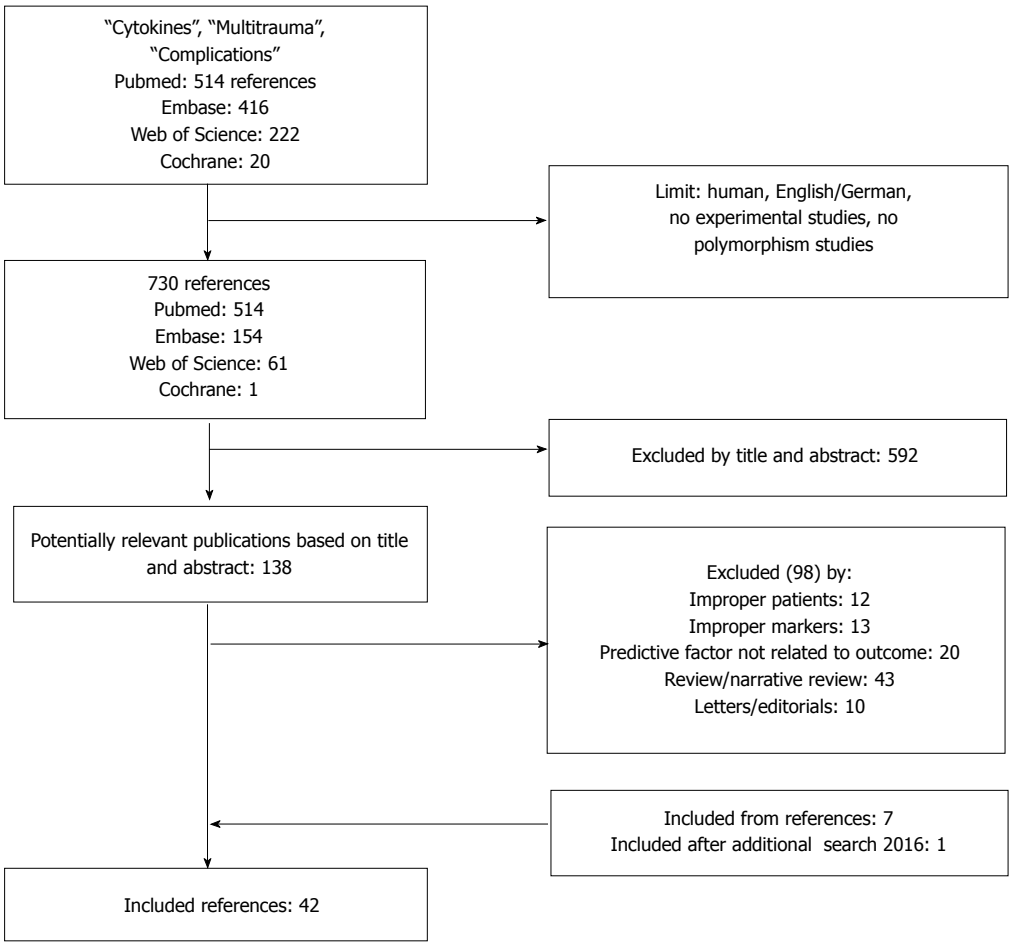

Figure 1 Results of the stepwise literature review procedure.

alterations in MOF. Twenty studies investigated the relation between cytokine concentrations and mortality. Only seven studies reported a cytokine cut-off value for the development of complications, five of which stated sensitivity (and specificity) for the cut-off value. Ten studies reported some kind of prediction value for the investigated cytokines (*i.e.*, odds ratio, area under the curve, sensitivity and specificity, 95%CI and positive/negative predictive value). All included studies are listed in Table 1. The overall study quality according to the STROBE statement was good, with a median total score of 18 points (range 12-24), suggesting a low risk of bias.

Value of main cytokine concentrations for predicting complications

IL-6: (1) ARDS; two studies[37,45] could not relate ARDS to IL-6 concentration alterations, whereas two other studies[48,51] found a positive correlation (Table 2); (2) Sepsis; five studies[35,41,46,47,53] found an increased IL-6 production to be predictive for the development of sepsis, whereas five other studies[28,29,38,39,55] did not (Table 3); (3) MODS; all five prospective cohort studies[3,28,34,46,51] concluded that IL-6 is markedly increased in the early development of MODS (Table 4); and (4) MOF; of the nine prospective studies, six[13,27,32,33,36,56] studies found a positive correlation between increased serum concentrations and development of MOF. Three[11,42,62] investigators demonstrated an elevated IL-6 in MOF patients, which was not predictive according to these studies (Table 5). Also, IL-6 tends to be higher in non-survivors (Table 6).

IL-8: (1) Two prospective cohort studies[37,48] reported a positive correlation between increased serum IL-8 concentrations and development of ARDS, whereas one[45] found no predictive value; (2) Two studies[38,55] reported that IL-8 was not significantly different between patients developing sepsis and those with an uneventful posttraumatic course; (3) One cohort study[3] found a higher IL-8 serum concentration in patients with MODS, which could however not predict the development of multiorgan dysfunction; and (4) Of the six included studies, four prospective studies[27,32,36,56] concluded that IL-8 is significantly higher in MOF. Two prospective studies[11,42] also found a significantly increased serum concentration, but concluded that this could not be translated into a predictive value for adverse outcome. Further, IL-8 concentrations seemed elevated in non-survivors.

Table 1 Overview of included studies, the studied cytokines and the outcome parameters (acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure, mortality)

No.	Ref.	Year	Design	No pts. (control)	Cytokines	ARDS (%)	Sepsis (%)	MODS (%)	MOF (%)	Mortality (%)
1	Billeter *et al*[35]	2009	P-coh	1032	IL-6					10%
2	Bogner *et al*[36]	2009	P-coh	58	IL-6, -8, -10				74%	19%
3	Cook *et al*[58]	2013	P-cc	83 (18)	G-CSF		7%			7%
4	Cuschieri *et al*[34]	2010	P-coh	152	IL-6			37%		5%
5	Donnelly *et al*[37]	1994	P-coh	15	IL-6, -8, -1β; TNF-α	49%				33%
6	Dresing *et al*[26]	2004	P-coh	30	IL-6; TNF-α			13%		19%
7	Egger *et al*[38]	2004	P-coh	26	IL-6, -8		35%			
8	Flores *et al*[39]	2001	P-coh	43	IL-6		49%			16%
9	Frangen *et al*[59]	2008	P-cc	71 (25)	IL-17, -6					22%
10	Frank *et al*[11]	2002	P-cc	77 (15)	IL-6, -8					9%
11	Frink *et al*[3]	2009	P-coh	143	IL-1β, -6, -8, -10; TNF-α		29%	17%		15%
12	Gebhard *et al*[40]	2000	P-coh	94	IL-6					19%
13	Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69 (10)	IL-6, -8; TNF-α, IFN-γ		62%			35%
14	Gouel-Chéron *et al*[53]	2012	P-cc	100 (18)	IL-6, -10		37%			5%
15	Haasper *et al*[28]	2010	P-coh	94	IL-6		16%	22%		13%
16	Hayakawa *et al*[31]	2011	P-coh	45	TNF-α			53%		25%
17	Heizmann *et al*[52]	2008	R-cc	195 (10)	IL-2, -4, -10, -11, -12, -18; IFN-γ					19%
18	Jastrow *et al*[32]	2009	P-coh	48	IL-6, -8, -10, -1β, -2, -4, -12; TNF-α				23%	17%
19	Keel *et al*[41]	2009	P-coh	83	IL-6		40%			12%
20	Lausevic *et al*[33]	2008	P-coh	65	IL-6, -10		62%		55%	51%
21	Lausevic *et al*[29]	2010	P-coh	65	IL-6, -10		63%			51%
22	Law *et al*[42]	1994	P-coh	13	IL-6, -8; TNF-α				46%	23%
23	Lendemans *et al*[13]	2004	P-coh	16	IL-6, -10; TNF-α				56%	
24	Liener *et al*[43]	2002	P-coh	94	IL-8	0%	0%		0%	19%
25	Livingston *et al*[44]	1988	P-coh	20	IFN-γ		30%			15%
26	Maier *et al*[27]	2007	P-coh	251	IL-6, -8, -10				34%	12%
27	Meade *et al*[45]	1994	P-coh	25	IL-6, -8; TNF-α	36%				
28	Menges *et al*[50]	1999	P-coh	68	IL-10, -1; TNF-α		25%		25%	1%
29	Mommsen *et al*[30]	2009	P-coh	55	IL-18		42%	13%		13%
30	Neidhardt *et al*[54]	1997	P-cc	417 (137)	IL-10	5%	11%	22%		22%
31	Oberholzer *et al*[46]	2000	P-coh	1276	IL-6, IL-10		14%	40%		7%
32	Partrick *et al*[56]	1996	P-cc	27 (6)	IL-6, -8				33%	7%
33	Paunel-Görgülü *et al*[47]	2011	P-coh	47 (17)	IL-6		38%			11%
34	Raymondos *et al*[48]	2012	P-coh	24	IL-6, -8, -1β, TNF-α	29%				4%
35	Roetman *et al*[60]	2008	P-cc	229 (110)	IL-18, -4; IFN-γ					16%
36	Schinkel *et al*[61]	2005	P-cc	216 (110)	IL-11				4%	16%
37	Sherry *et al*[14]	1996	R-cc	66 (10)	IL-10	8%	39%			2%
38	Sousa *et al*[51]	2015	P-coh	99	IL-6, -10; TNF-α	19%		34%		28%
38	Spielmann *et al*[57]	2001	P-cc	47 (15)	TNF-α	11%	30%	51%		23%
39	Svoboda *et al*[62]	1994	P-cc	42 (12)	IL-1β, -2, -6; TNF-α				33%	26%
40	Wick *et al*[49]	2000	P-coh	37	IL-12			11%		16%
41	Yagmur *et al*[63]	2005	P-cc	99 (10)	IL-1, -2, -6, -8; TNF-α					17%

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Pts: Patients; Y: Yes; N: No.

IL-10: (1) Three studies, two prospective[54,57] and one retrospective[14], could not relate the serum IL-10 concentrations to the development of ARDS. One study[51] found IL-10 to be significantly higher in patients with ARDS; (2) Of the five reviewed studies, three prospective[29,50,54] and one retrospective study[14] found the IL-10 concentration to be predictive for the development of sepsis, whereas one prospective study[53] did not; (3) Two studies[51,54] reported IL-10 to be significantly elevated in patients with MODS, and two studies[3,57] could not find an association between the cytokine and development of MODS; and (4) According to five studies[13,32,33,36,50] the serum IL-10 concentration was significantly higher in MOF patients. One study showed no significant elevation[27].

TNF-α: (1) Three studies found no relation between TNF-α and development of ARDS[37,45,51]; (2) One study[55] concluded that concentrations were not related to development of sepsis, while one study[50] found significantly increased concentrations in septic patients; (3) Of the four studies reporting on TNF-α concentrations after trauma, two studies[31,51] found TNF-α to be related to the development of MODS, and two studies[3,57] could not relate serum concentrations

Table 2 Value of cytokine concentrations for predicting acute respiratory distress syndrome

Ref.	Year	Design	No pts.	ARDS *n* (%)	Predicts ARDS	Results
IL-6						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-6] is not significantly different in ARDS
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-6] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-6] is significantly higher in patients at high risk for ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-6] is significantly higher at 72 h post injury
IL-8						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	Y	[IL-8] is significantly higher in patients with ARDS, starting at 16 h post injury
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-8] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-8] is significantly higher in patients at high risk for ARDS
IL-10						
Neidhardt *et al*[54]	1997	P-cc	417	19 (5%)	N	[IL-10] is not related to the development of ARDS
Sherry *et al*[14]	1996	R-cc	66	5 (8%)	N	[IL-10] is not related to the development of ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-10] is significantly higher in patients with ARDS upon admission, at 24 + 48 + 72 h post injury
Spielmann *et al*[57]	2001	P-cc	47	5 (11%)	N	[IL-10] is not related to the development of ARDS
TNF-α						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[TNF-α] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[TNF-α] below detection limit
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	N	[TNF-α] is not related to the development of ARDS
IL-1β						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-1β] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-1β] below detection limit

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; Pts: Patients; Y: Yes; N: No.

Table 3 Value of cytokine concentrations for predicting sepsis

Ref.	Year	Design	No pts.	Sepsis *n* (%)	Diagnostic tests	Predicts sepsis	Results
IL-6							
Billeter *et al*[35]	2009	P-coh	1032			Y	[IL-6] is significantly higher in sepsis between days 3-7
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-6] is significantly higher in sepsis before clinical manifestations; does not predict sepsis
Flores *et al*[39]	2001	P-coh	43	21 (49%)		N	[IL-6] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	ROC AUC 0.500 (95%CI: 0.304-0.696, $P > 0.05$)	N	[IL-6] is not related to the development of sepsis
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)	> 67.1 pg/mL: Sensitivity 85%; specificity 73%	Y	[IL-6] > 67.1 pg/mL is predictive for sepsis on days 1 + 2 (OR = 10.9)
Haasper *et al*[28]	2010	P-coh	94	15 (16%)		N	[IL-6] is not significantly different in sepsis
Keel *et al*[41]	2009	P-coh	83	33 (40%)		Y	[IL-6] is significantly higher in sepsis on days 5 + 14
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		N	[IL-6] is not predictive for sepsis
Oberholzer *et al*[46]	2000	P-coh	1276	179 (14%)		Y	[IL-6] is significantly higher in septic patients
Paunel-Görgülü *et al*[47]	2011	P-coh	47	18 (38%)	AUC ROC 0.79 (day 5 post injury)	Y	[IL-6] is significantly elevated on days 5 + 9 in sepsis
IL-8							
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-8] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.453 (95%CI: 0.254-0.652, $P > 0.05$)	N	[IL-8] is not predictive for sepsis
IL-10							
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)		N	[IL-10] is not related to the development of sepsis
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		Y	[IL-10] is significantly lower in sepsis on days 1 + 2
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d

Neidhardt *et al*[54]	1997	P-cc	417	45 (11%)		Y	[IL-10] is significantly higher in sepsis on days 1 + 3 + 5 + 7 + 10 + 14 + 21
Sherry *et al*[14]	1996	R-cc	66	26 (39%)		Y	[IL-10] is significantly higher in sepsis
TNF-α							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.466 (95%CI: 0.274-0.657, $P > 0.05$)	N	[TNF-α] is not related to the development of sepsis
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
IFN-γ							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)		N	[IFN-γ] below detection limit
Livingston *et al*[44]	1988	P-coh	20	6 (30%)		Y	[IFN-γ] is markedly lower in sepsis after 14 d
G-CSF							
Cook *et al*[58]	2013	P-cc	83	6 (7%)		Y	[G-CSF] > 500 pg/mL is significantly associated with sepsis
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	23 (42%)		Y	[IL-18] is significantly higher in sepsis on days 3-6 post injury
IL-1							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; Pts: Patients; Y: Yes; N: No.

Table 4 Value of cytokine concentrations for predicting muli-organ dysfunction syndrome

Study	Year	Design	No pts.	MODS *n* (%)	Diagnostic tests	Predicts MODS	Results
IL-6							
Cuschieri *et al*[34]	2010	P-coh	152	29 (37%)	> 350 pg/mL: Sensitivity 79%, specificity 76%; OR = 3.87 (95%CI: 1.13-11.19)	Y	[IL-6] > 350 pg/mL is highly associated with MODS
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.35$; > 761.7 pg/μL: Sensitivity 16.7%, specificity 98.3%	Y	[IL-6] > 76.6 pg/μL is associated with MODS with accuracy of 84.7%
Haasper *et al*[28]	2010	P-coh	94	21 (22%)		Y	[IL-6] is significantly higher in MODS on days 1 + 7
Oberholzer *et al*[46]	2000	P-coh	1276	516 (40%)		Y	[IL-6] is significantly higher in (severe) MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 294 pg/mL: AUC ROC 0.769 (95%CI: 0.414-0.736)	Y	[IL-6] > 294 pg/mL is associated with MODS at 48 + 72 h post injury
IL-8							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.53$; sensitivity 0%	N	[IL-8] is significantly higher in MODS; does not predict development of MODS
IL-10							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.31$; sensitivity 0%	N	[IL-10] is significantly higher in MODS; does not predict development of MODS
Neidhardt *et al*[54]	1997	P-cc	417	92 (22%)		Y	[IL-10] is significantly higher in MODS on days 1 + 3 + 5 + 7 + 10 + 14 + 21 post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[IL-10] is not related to the development of MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 4.93 pg/mL: AUC ROC 0.700 (95%CI: 0.506-0.841)	Y	[IL-10] > 4.93 pg/mL is associated with MODS at 24 + 72 h post injury
TNF-α							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.32$; sensitivity 0%	N	[TNF-α] is significantly higher in MODS; does not predict development of MODS
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[TNF-α] is significantly higher in MODS on days 3 + 5
Sousa *et al*[51]	2015	P-coh	99	34 (34%)		Y	[TNF-α] is associated with MODS at 48 h post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[TNF-α) is not associated with MODS
IL-1β							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.00$; sensitivity 0%	N	[IL-1β] is not related to development of MODS
IL-12							
Wick *et al*[49]	2000	P-coh	37	4 (11%)		Y	[IL-12] is significantly lower in patients with MODS
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	7 (13%)		Y	[IL-18] is significantly higher in MODS on days 2 + 3 + 6 + 7 + 9 + 10 + 13 + 14
MIF							
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[MIF] is significantly higher in MODS

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MODS; MODS: Muli-organ dysfunction syndrome; Pts: Patients; Y: Yes; N: No.

Table 5 Value of cytokine concentrations for predicting multi-organ failure

Ref.	Year	Design	No pts.	MOF *n* (%)	Diagnostic tests	Predicts MOF	Results
IL-6							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-6] is significantly higher in MOF at 0 - 24 + 72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.25 on day 2	N	[IL-6] is significantly higher in MOF; no reliable predictor due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.816; (IL-6) > 0.861 pg/mL: sensitivity 57%, PPV 100%	Y	[IL-6] > 0.861 pg/mL is highly predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-6] is significantly higher in MOF on all days of hospitalization
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-6] is significantly higher in MOF after two weeks
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-6] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.70 for late-onset MOF	Y	[IL-6] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-6] is significantly higher in MOF at 12 + 36 h
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-6] is higher in MOF at day 1, does not predict MOF
IL-8							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-8] is significantly higher in MOF from 0-72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.32 on day 2	N	[IL-8] is significantly higher in MOF; not reliable due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[IL-8] is significantly higher in MOF from 0-24 h
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-8] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.69 for late-onset MOF	Y	[IL-8] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-8] is significantly higher in MOF at 12 + 36 + 84 h
IL-10							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-10] is significantly higher in MOF in early post-injury phase (< 12 h)
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.776; (IL-10) > 38.6 pg/mL: Sensitivity 71%, PPV 77%	Y	[IL-10] > 38.6 pg/mL is predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-10] is significantly higher in MOF in very early post injury phase
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-10] is significantly higher in MOF on days 3 + 4
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.60 for late-onset MOF	N	[IL-10) is not predictive for MOF
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d
TNF-α							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[TNF-α] is significantly higher in MOF from 2 – 6 + 10 – 24 h
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[TNF-α] is significantly higher in MOF on days 7 + 8 + 10 + 11
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
Svoboda *et al*[62]	1993	P-cc	42	14 (33%)		Y	[TNF-α] is higher in MOF, but only after onset of symptoms
IL-1(β)							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13
Svoboda *et al*[62]	1994	P-xx	42	14 (33%)		N	[IL-1β] is not related to MOF
IL-2							
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-2] is not related to MOF
IP-10							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 889.9 pg/mL has a sensitivity of 71% and PPV of 100%	Y	[IP-10] is highly predictive for MOF (AUC ROC 0.939)
Eotaxin							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 193.8 pg/mL has a sensitivity of 71% and PPV of 62%	Y	[Eotaxin] is highly predictive for MOF (AUC ROC 0.810)
MIP-1β							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 248.6 pg/mL has a sensitivity of 71% and PPV of 77%	Y	[MIP-1β] is highly predictive for MOF (AUC ROC 0.871)
IL-11							
Schinkel *et al*[61]	2005	P-cc	216	9 (4%)		N	[IL-11[is not significantly different in MOF

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MOF; PPV: Positive predictive value; MOF: Multi-organ failure; Pts: Patients; Y: Yes; N: No.

Table 6 Value of cytokine concentrations for predicting mortality

Ref.	Design	No pts.	Mortality *n* (%)	Follow-up	Diagnostic tests	Predicts mortality	Results
IL-6							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-6] is significantly higher in non-survivors at 0 + 6 h
Cuschieri *et al*[34]	P-coh	152	4 (5%)	In-hospital		N	[IL-6] is not significantly higher in non-survivors
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		Y	[IL-6] is significantly higher in non-survivors on days 3 + 5
Frink *et al*[3]	P-coh	143	21 (15%)	In-hospital	> 2176.0 pg/mL: Sensitivity 28.6%, specificity 100% on day 1	Y	[IL-6] is highly predictive for non-survival (AUC ROC 0.858)
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors
Gebhard *et al*[40]	P-coh	94	18 (19%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors at 4 + 6 + 12 h post injury
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.60	N	[IL-6] is not predictive for non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 276 pg/mL: AUC ROC2 0,775 (95%CI: 0.591-0.960)	Y	[IL-6] > 276 pg/mL is significantly correlated with non-survival
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	> 400 pg/mL has a sensitivity of 100%	Y	[IL-6] > 400 pg/mL is significantly correlated with non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-6] is significantly elevated in non-survivors
IL-8							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-8] is significantly higher in non-survivors at 6 + 24 h
Liener *et al*[43]	P-coh	94	18 (19%)	15 d		Y	[IL-8] is significantly higher in non-survivors from 30 min-24 h
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.45	N	[IL-8] is not predictive for non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-8] is significantly elevated in non-survivors
IL-10							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-10] is significantly higher in non-survivors at 72 h post injury
Gouel-Chéron *et al*[53]	P-cc	100	5 (5%)	14 d		Y	[IL-10] is significantly higher in non-survivors when detectable on days 1 + 2
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-10] tends towards lower levels in non-survivors; not significant
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.51	N	[IL-10] is not predictive for non-survival
Neidhardt *et al*[54]	P-cc	417	92 (22%)	21 d		Y	[IL-10] is significantly increased in non-survivors on days 1 + 3
Sherry *et al*[14]	R-cc	66	1 (2%)	50 d		N	[IL-10] is not related to non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 8.24 pg/mL: AUC ROC 0.871 (95%CI: 0.715-1.000)	Y	[IL-10] > 8.24 pg/mL is associated with non-survival at 48 + 72 h post injury
TNF-α							
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		N	[TNF-α] is not significantly elevated in non-survivors
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h		N	[TNF-α] is not significantly elevated in non-survivors
Spielmann *et al*[57]	P-cc	47	11 (23%)	6 d		N	[TNF-α] is not significantly elevated in non-survivors
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		Y	[TNF-α] is significantly elevated in non-survivors
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		N	[TNF-α] is not significantly elevated in non-survivors
IL-18							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-18] tends towards lower levels in non-survivors; not significant
Mommsen *et al*[30]	P-coh	55	7 (13%)	14 d		Y	[IL-18] is significantly increased in non-survivors on days 2-7
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d		N	[IL-18] median value is significantly lower in non-survivors
IL-2							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-2] tends towards lower levels in non-survivors; not significant
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		N	[IL-2] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-2] is significantly increased in non-survivors
IL-1							

Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	N	[IL-1] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d	N	[IL-1] is not related to non-survival
IL-12						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-12] tends towards lower levels in non-survivors; not significant
Wick *et al*[49]	P-coh	37	6 (16%)	In-hospital	Y	[IL-12] is significantly lower in non-survivors
IL-11						
Schinkel *et al*[61]	P-cc	216	34 (16%)	In-hospital	N	[IL-11] is lower in non-survivors, only reaching significance after week 4
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-11] tends towards lower levels in non-survivors; not significant
IL-17						
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital	N	[IL-17] is not related to non-survival
IL-4						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-4] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IL-4] is not related to mortality
IFN-γ						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IFN-γ] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IFN-γ] inconsistently detectable

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; AUC: Area under the receiver operating characteristic (ROC) curve; Pts: Patients; Y: Yes; N: No.

to MODS; and (4) Four studies[13,32,50,62] showed that patients with MOF had significantly higher TNF-α concentrations compared to patients with uneventful course, although Svoboda *et al*[62] found no predictive value for the cytokine.

DISCUSSION

Polytraumatized patients are at risk for the development of various complications, leading to considerable morbidity and mortality. Early identification of "high risk" patients could improve outcome after accidental injury, because physicians are directed to the appropriate treatment. Further, close monitoring of the immune response could direct physicians to the appropriate timing of surgical interventions, thereby reducing "second hits" with subsequent development of sepsis and organ failure. The aim of the present review was to summarize the knowledge on cytokines predicting the development of ARDS, sepsis, MODS, MOF and mortality. According to the investigated studies, some cytokines seem to predict specific complications: Patients with ARDS seem to have higher IL-8 concentrations; IL-10 secretion seems increased in septic patients; and MODS/MOF development is preceded by an enhanced IL-6, IL-8, IL-10, and TNF-α release. With respect to the other cytokines studied (IFN-γ, G-CSF, IL-1β, -2, -4, -11, -12, -17, -18, MIF, MIP-1β, eotaxin, IP-10), study results are either inconsistent, or the small amount of current evidence makes an objective conclusion for the present study impossible.

IL-6

Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β)[7,8]. It is liberated after tissue damage and infection. The relatively late release and long half-life of IL-6 renders the cytokine a convenient parameter for clinical monitoring of the immune response of individual patients. The conflicting results of the reviewed studies lead to the conclusion that IL-6 cannot be used as a marker for ARDS and sepsis; elevated IL-6 concentrations do appear to precede the development of MODS, MOF and mortality. In future, physicians might therefore use IL-6 as a predictor of MODS, MOF and mortality in polytraumatized patients.

IL-8

IL-8 induces expression of adhesion molecules, thereby enabling migration of neutrophils to the site of production[4,9]. Production of IL-8 takes place early in the inflammatory response and can persist for days or weeks[13]. According to the reviewed studies, IL-8 is higher in patients developing ARDS, MOF and in non-survivors. Of note, when IL-8 is used to investigate the development of ARDS, measuring local concentrations in bronchoalveolar lavage fluid generally leads to earlier identification of patients at risk[64-67]. The causal relation between the chemotaxis IL-8 exerts on PMN's, and subsequent autodestructive changes in remote organs leading to ARDS and MOF[64], likely explains the consistent results of included studies. In line with these results, IL-8 might be used to identify patients prone to develop ARDS and MOF. Such a predictive value could not be demonstrated for the development of sepsis and MODS.

IL-10

IL-10 decreases cytokine production of T_H1 cells and reduces antigen presentation of macrophages and subsequent proliferation of T lymphocytes[14]. Release of high amounts of IL-10 occurs rapidly, generally within 60 min after trauma[54]. According to our study, an

enhanced IL-10 secretion is related to the development of sepsis and MOF. Clearly, a vigorous anti-inflammatory IL-10 release makes the host susceptible to infections with subsequent sepsis and (sepsis-related) MOF. Therefore, IL-10 concentrations might direct physicians to the patients prone to develop sepsis and MOF. Concentrations of IL-10 could not be related to the development of ARDS, MODS and mortality.

TNF-α

The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma[4]. Peak concentrations of TNF-α can be observed within one to two hours after trauma. Previous studies have demonstrated a positive correlation between elevated TNF-α and poor outcome[68-70]. However, as reported in this review, the elevation of TNF-α could only be related to the development of MOF. This might be explained by the very short half-time of the cytokine (14-18 min), suggesting that peak concentrations early in the posttraumatic course have already returned to baseline by the time a septic event and subsequent organ failure is recognized[2,9,13].

Other cytokines

According to Cook *et al*[58], elevation of G-CSF significantly related to the development of hospital-acquired pneumonia. Wick *et al*[49] demonstrated that all patients with continuous decreased IL-12 levels died from septic MOF; comparable findings were demonstrated by Hensler *et al*[71]. Increased IL-12 production could, however, have unfavorable effects as well[72,73]. According to previous studies, IL-18 release is significantly correlated with sepsis, and its activation might be enhanced after infiltration of micro-organisms[74,75]. This effect could also be demonstrated by Mommsen *et al*[30]. Jastrow *et al*[32] determined a predictive value for several cytokines, among which IP-10, MIP-1β and eotaxin appear to be most accurate. More research has to be done before the value of these cytokines can be reviewed.

Limitations

The principal limitation in this study was the heterogeneity across studies in terms of patient population, study design and statistical techniques used. Hence, meta-analysis of presented data could not be performed. Further, variations between patients in an individual study can result from differences in injury severity or injury pattern, diverse individual immunologic responses (gene polymorphisms), and general confounders such as age, sex, pre-existing diseases, number and amount of administrated therapeutic agents and secondary surgery. These aspects were not clearly outlined in most of the included studies. All these factors may alter the individual inflammatory response, and contribute to a low correlation between investigated cytokine and certain complication. Further, only a small amount of studies for each biomarker-complication combination was selected, due to the very specific research question. This made it difficult to draw clear conclusions from presented results. Also, some studies reported predictive values for the ratio of different cytokines. According to these studies, complications could be predicted more accurately when combining several cytokines in one prediction model. However, we could not include these findings in our results because of the small amount of studies investigating these specific ratios. Additionally, systemic concentrations of cytokines not necessarily reflect concentrations in end-organs. It might therefore be well possible that local concentrations of cytokines can more accurately predict the development of complications. Despite these concerns, the results presented in this review can be useful in the clinical appraisal of critically ill patients. For future studies on cytokines and polytrauma patients, we recommend the development of specific polytrauma protocols. Implementation of such protocols provides the possibility for meta-analysis in the future, as previously mentioned confounding factors would then be handled similarly. Important confounding factors that most studies did not elaborate on, include amount of resuscitation fluids administered, length of mechanical ventilation, need for nutritional support and secondary surgery. Monitoring cytokine secretion patterns without considering these factors, would give an unrealistic representation of posttraumatic immune alterations. Therefore, more research is needed to better understand the specific role of these factors in the individual immune response to trauma.

In conclusion, this article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death. According to the current review, cytokine secretion patterns are different for patients developing complications, compared to patients with an uneventful posttraumatic course. Some of these cytokines, such as IL-6, IL-8 and IL-10, seem to be of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

COMMENTS

Background

Severe trauma represents the most frequent cause of death in people below the age of 45. Early identification of patients at risk for developing complications is one of the most challenging problems in the treatment of multiple injuries. Close monitoring of cytokine secretion patterns may provide physicians with an impression of the patients' risk for developing complications. Further, cytokine secretion patterns may pose an indication for the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing the risk of sepsis and multiorgan failure. The aim of the current review was: (1) to summarize the available knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure and mortality.

Research frontiers

Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Over the past 20-25 years, cytokines have gained attention in the understanding of the posttraumatic pathophysiological immune alterations. Cytokines play a pivotal role in the pro- and anti-inflammatory reaction to trauma, and are essential in the subsequent defence and repair mechanisms. As cytokines serve as messenger molecules in cell-to-cell communication, they are likely to play an important role in the development of posttraumatic complications such as sepsis and multi organ failure.

Innovations and breakthroughs

Previous studies have acknowledged the correlation between cytokine concentrations and patients' clinical condition after polytrauma. Yet, specific predictors for the development of posttraumatic complications have not been identified. The available literature concerning the relation between cytokine concentrations and development of posttraumatic complications was systematically reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that interleukin (IL)-6, IL-8 and IL-10 are of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

Terminology

SIRS: Systemic inflammatory response syndrome, defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992; ARDS: Acute respiratory distress syndrome, determined in concordance with the American-European Consensus Conference 1994 definitions; Sepsis: Diagnosed when SIRS occurs in combination with a septic focus or positive blood culture; MODS and MOF: Multi-organ dysfunction syndrome/multi-organ failure, diagnosed based on different scoring systems.

Peer-review

This is an excellent literature analysis on an important issue. The paper was very well-structured and written.

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