Article:
Ahmed, S, Wilcox, M and Kirby, A (2020) Measuring outcomes in complicated intra-abdominal infections. Current Opinion in Gastroenterology, 36 (1). pp. 1-4. ISSN: 0267-1379

https://doi.org/10.1097/MOG.0000000000000591

Title: Measuring outcomes in complicated intra-abdominal infections

Author names: Shadia Ahmed[1,2], Mark Wilcox[1,2], Andrew Kirby[1,2]

Author Affiliations:

1. Department of Microbiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

2. University of Leeds, Leeds, UK

Corresponding author: Shadia Ahmed. Old Medical School, Leeds General Infirmary, Leeds, LS1 3EX. E-mail: shadiaahmed@nhs.net, Telephone: +44 (0)113 3923929

Abstract

Purpose of review

Complicated intra-abdominal infections (cIAIs) are associated with significant morbidity and mortality. Clinical trials should help guide and improve the management of cIAIs. However, inappropriate selection or measurement of outcomes in cIAIs clinical trials can lead to misleading results on the effectiveness of interventions. This review aims to describe how outcomes are reported in randomised controlled trials (RCTs) evaluating antibiotic treatment for cIAIs and discuss how outcome reporting may be improved.

Recent findings

Commonly used primary outcomes are treatment success or failure, these outcomes are endorsed by regulatory bodies. However, a consensus objective definition of either is not available and current measures are prone to bias. Variation exists in timing of outcome evaluation and analysis populations which can lead to further bias. Use of core outcome sets (COS) can help standardise outcome reporting.

Summary

Inconsistency in outcome selection and reporting can lead to misleading results and impedes meta-analysis of data. Further progress, engaging clinical trialists, regulatory authorities, clinicians and patients is required to achieve consensus on which outcomes should be reported and how and when to measure them.

Keywords

Complicated intra-abdominal infections, Clinical trials, Outcome measures, Core outcome sets

Key Points

- There are variations in the selection and measurements of outcomes in clinical trials assessing antibiotics and antibiotic treatment strategies for complicated intra-abdominal infections (cIAIs).
- These variations can lead to difficulty in interpreting trial results and impedes comparison of different studies.
- Development of a core outcome set to be used in cIAIs trials, will standardise the outcome used and lead to higher quality evidence generation, enabling to clinicians to make better decisions on the management of cIAIs.

Introduction

Complicated intra-abdominal infections (cIAIs) are intra-abdominal infections that have extended beyond the organ of origin causing either abscess formation and/or peritonitis (1). They are the second commonest cause of sepsis in patients on intensive care units (2, 3). A recent six month prospective study of cIAIs worldwide reported a 10.5% mortality in patients with cIAIs (4). Management of cIAIs includes controlling the source of infection (through either a surgical procedure or percutaneous

drainage of an abscess) plus systemic antibiotic therapy. As resistance to commonly used antibiotics in cIAIs rises, clinical trials assessing the effectiveness of new antibiotics for cIAIs are essential.

Outcome measures are used in research to help to determine the comparative efficacy of different interventions and treatments. However, while the choice of outcomes often seem obvious to clinicians (e.g. failure of treatment), it is in practice a difficult challenge to define clear, reproducible and widely agreed outcomes. This matters, as unsuitable or poorly defined outcomes could lead to inappropriate conclusions about the safety and/or efficacy of an intervention. It is also well recognised that inconsistent and incomplete outcome reporting is common, making the interpretation of the effectiveness of different interventions difficult (5). Additionally, consistent outcomes are needed to allow meta-analyses to be performed. To ensure consistent outcomes are collected in randomised clinical trials (RCTs), it is recommended a set of core outcomes should be collected (6). Core outcomes are an agreed minimum number of outcomes that should be reported in all trials for a specific condition. Initiatives such as COMET (Core Outcome Measures in Effectiveness Trials) provides a resource to search for developed and in preparation core outcome sets (6).

In antibiotic trials for complicated intra-abdominal infections, the dichotomous outcome of cure/failure is often reported. However, a consensus definition of 'cure' does not exist and it is often based on subjective measures. Additionally, these dichotomous outcomes are of limited value as they do not take into account a patient's global experience of benefits and harms, as well as the impact on quality of life. Furthermore, when, how, and in which analysis population outcomes are measured need to be considered, otherwise there is considerable scope for bias and inaccurate conclusions of management efficacy and safety.

This review summarises the current recommended outcomes and the outcomes measured in recent and landmark trials assessing antibiotic treatment for complicated intra-abdominal infections. Recommendations on future measures to improve outcome reporting in cIAIs are also provided.

Outcome selection

In 1990, Nystrom et al. proposed a set of outcomes to be used in clinical trials of the management of intra-abdominal infections (7). The proposed primary outcomes were mortality and time to recovery. They define recovery as restoration of normal physiology (as indicated by a acute physiology score), a temperature <37.8^{o}C for 24 hours, restoration of gastrointestinal function (as demonstrated by ability to tolerate an oral diet), return of gastrointestinal motor activity (as indicated by passing of flatus or faeces) and that the patient is alert and orientated (or returned to baseline). The authors stated that time to recovery is preferred over the more subjective measures of cured, improved or failed outcomes, as it is objective and easily measurable using the above criteria.

The Food and Drug Administeration (FDA) and European Medicines Agency (EMA) require antibiotic efficacy trials, which aim to generate evidence for the approval of a new agent, to report on specific outcomes, as outlined in their respective guidelines (8, 9). In the FDA guidance, it is recommended that clinical success or failure should be assessed as primary outcomes, with assessments up until day 28 post randomisation (8). Clinical success is defined as the 'resolution of baseline signs and symptoms' based on objective measures. Clinical failure is classed as either death, the need for a unplanned surgical procedure, an extra-abdominal infection, surgical site infection (SSI) or relapse (or worsening) of cIAI. The EMA recommends that clinical outcome, categorised as cure, failure or indeterminant,

should be reported as the primary outcome. Cure is described as the complete resolution of clinical signs and symptoms; however, it is not specified which parameters should be measured, but that outcome evaluation should occur at an appropriately timed test of cure (TOC) visit (9).

Different analysis populations are used to report outcomes in clinical trials of cIAIs treatments. Commonly used analysis populations include the modified intention to treat (mITT) population (defined as all trial participants who received the intervention), clinically evaluable (CE) population (which generally includes patients who have received the intervention as per protocol and adhered to all study procedures) and the microbiological intention to treat (micro-ITT) population (which includes participants who fulfil CE criteria and who also have a baseline bacterial pathogen known to cause cIAI) (10). The FDA and EMA both now suggest that the micro-ITT should be used as the primary analysis population (8, 9). Analysis of specific populations can lead to bias as it excludes some patients, and so may fail to retain the balance of participant numbers in each trial arm created by baseline randomisation. However, where ITT populations are very similar to the CE, mITT and micro-ITT populations the risk of bias is negligible (10).

More recently, the potential merits of an innovative outcome ranking (DOOR) scale for evaluating treatment outcomes for antibiotic studies have been described (11). This ordinal scale (i.e. the second level of measurement that reports the ranking and ordering of data without actually establishing the degree of variation between them) categorises participants into clinical outcomes based on both the benefits and harms they experience, and then ranks these according to the desirability of each outcome. Higher ranks are assigned to participants with better clinical outcomes. The benefit of using DOOR is that it attempts to analyse a patient's global experience by combining efficacy and safety outcomes (12). DOOR can be used with the 'response adjusted for duration of antibiotic risk' (RADAR), which is a tool to measure antibiotic use. Like DOOR, it has an ordinal scale and it assumes that shorter antibiotic courses are superior. Participants in each DOOR category are further ranked based on their RADAR score. Finally, the probability that a participant will have a better DOOR/RADAR score if assigned to the intervention arm is then calculated. Celestin et al, in a post hoc analysis applied DOOR/RADAR to data from the STOP IT trial, which evaluated antibiotic duration for cIAIs; short course antibiotics were found to be superior to longer courses (13, 14). However, selection of the DOOR/RADAR components is subjective and may differ between trials. Furthermore, studies have found that the final DOOR/RADAR scores are influenced by the number of clinical outcome categories (11, 13, 15). Therefore, it is important that these categories are selected carefully a-priori via a consensus process.

Current guidance fails to identify the best approach to selecting and measuring outcomes. The FDA and EMA guidelines do not offer guidance on how to measure treatment success, therefore different parameters may be used by different trialists. Alternatively, Nystrom et al, suggest using time to cure as an objective measure of treatment success however this is not utilised (16-19). Although, DOOR/RADAR is an alternative to traditional binary outcomes, its role in cIAIs trials needs further review.

Currently reported outcomes

In 2017, IGNITE 1, a randomised control trial (RCT) that compared the novel synthetic tetracycline evracycline with ertapenem, the primary outcome used was clinical response (clinical cure, failure or indeterminate) in the micro-ITT group at the TOC visit performed 25-31 days after randomisation

(16).Cure was defined as the complete resolution or significant improvement in all signs and symptoms of the index infection such that no further antibiotics or intervention was required. Failure was defined as either death related to cIAI at any time, the persistence of signs or symptoms, unplanned procedures, SSI or the initiation of additional antibiotics for cIAI. The primary outcomes were reported in modified-ITT, CE and micro-ITT populations in order to comply with regulatory guidance. IGNITE 4 (2018) compared evracycline with meropenem, this trial design was similar to IGNITE 1 and the same outcome measures were used (17). Qin et al (2017), similarly used clinical response as the primary efficacy outcome in their RCT comparing ceftazidime/avibactam plus metronidazole with meropenem in patients with cIAIs in Asia (18). The analysis population was the clinically evaluable (CE) population with outcome assessments occurring 28-35 days after randomisation. In a multicentre RCT comparing tigecycline with imipenem/cilastatin to treat cIAIs, Chen et al (2018) also used the CE population as the primary analysis population to report their primary outcome of clinical cure, which was assessed at the TOC visit performed between 14 - 21 days after end of treatment (EOT) (19). Evidently, each of these studies assessed outcomes at different time points (14-21 days vs 25-31 days vs 28-35 day), and such inconsistency could lead to bias.

The landmark STOP IT trial published in 2015 compared short course (4 days +/- 1 day) with long course (≤ 10 days) antibiotics for cIAIs (14). Ongoing signs of a systemic inflammatory response (SIRS) in the group who received short course antibiotic was not indicative of clinical failure, and instead was suggested by the investigators to be a marker of host immune activity. Thus, using resolution of symptoms and signs could be an unreliable marker of clinical response. This RCT was the first to assess antibiotic duration for cIAIs. The primary outcome was a composite consisting of SSI, recurrent cIAI, or death occurring within 30 days of the primary source control procedure. In a subsequent RCT evaluating antibiotic duration for patients with post-operative cIAIs, the DURAPOP trial (2018), the investigators used antibiotic free days as assessed on day 28 as the primary outcome (20). Although antibiotic free days can be a proxy marker for efficacy, it is not a patient centred outcome. Initially there were two proposed primary outcomes (antibiotic free days between days 8 and 45 and mortality between days 8 and 45). However, due to low recruitment rates this was switched to a single outcome, thus illustrating how the choice of outcomes measured can be affected by study design.

Conclusion

There are variations in the outcomes used in antimicrobial trials for cIAI, as well as how and in whom these are assessed. Albeit potentially subtle, such differences have the potential to lead to bias resulting in misleading results and failure to find the best treatment to improve patients' quality of life. This, coupled with the lack of objective and validated definitions, means that the current outcomes used in cIAIs are flawed. The development and implementation of standardised outcomes, so called 'core outcome sets', that are clinically meaningful would allow a more accurate understanding the effectiveness of different treatments for cIAIs. This would enable clinicians to make better decisions on patient care, and result in improved antimicrobial prescribing and patient experience. Regulatory bodies should promote the development of core outcome sets for use in future clinical trials.

Word count: 1808

References

1. Solomkin, J.S., Mazuski, J.E., Bradley, J.S., Rodvold, K.A., Goldstein, E.J., Baron, E.J., O'Neill, P.J., Chow, A.W., Dellinger, E.P., Eachempati, S.R., Gorbach, S., Hilfiker, M., May, A.K., Nathens, A.B., Sawyer, R.G. and Bartlett, J.G. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2010, **50**(2), pp.133-164.
2. Inui, T., Haridas, M., Claridge, J.A. and Malangoni, M.A. Mortality for intra-abdominal infection is associated with intrinsic risk factors rather than the source of infection. *Surgery.* 2009, **146**(4), pp.654-661; discussion 661-652.
3. Brun-Buisson, C., Doyon, F., Carlet, J., Dellamonica, P., Gouin, F., Lepoutre, A., Mercier, J.C., Offenstadt, G. and Regnier, B. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. *JAMA.* 1995, **274**(12), pp.968-974.
4. Sartelli, M., Catena, F., Ansaloni, L., Coccolini, F., Corbella, D., Moore, E.E., Malangoni, M., Velmahos, G., Coimbra, R., Koike, K., Leppaniemi, A., Biffl, W., Balogh, Z., Bendinelli, C., Gupta, S., Kluger, Y., Agresta, F., Di Saverio, S., Tugnoli, G., Jovine, E., Ordonez, C.A., Whelan, J.F., Fraga, G.P., Gomes, C.A., Pereira, G.A., Yuan, K.C., Bala, M., Peev, M.P., Ben-Ishay, O., Cui, Y., Marwah, S., Zachariah, S., Wani, I., Rangarajan, M., Sakakushev, B., Kong, V., Ahmed, A., Abbas, A., Gonsaga, R.A., Guercioni, G., Vettoretto, N., Poiasina, E., Diaz-Nieto, R., Massalou, D., Skrovina, M., Gerych, I., Augustin, G., Kenig, J., Khokha, V., Trana, C., Kok, K.Y., Mefire, A.C., Lee, J.G., Hong, S.K., Lohse, H.A., Ghnnam, W., Verni, A., Lohsiriwat, V., Siribumrungwong, B., El Zalabany, T., Tavares, A., Baiocchi, G., Das, K., Jarry, J., Zida, M., Sato, N., Murata, K., Shoko, T., Irahara, T., Hamedelneel, A.O., Naidoo, N., Adesunkanmi, A.R., Kobe, Y., Ishii, W., Oka, K., Izawa, Y., Hamid, H., Khan, I., Attri, A., Sharma, R., Sanjuan, J., Badiel, M. and Barnabe, R. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. *World J Emerg Surg.* 2014, **9**, p.37.
5. Dwan, K., Altman, D.G., Arnaiz, J.A., Bloom, J., Chan, A.W., Cronin, E., Decullier, E., Easterbrook, P.J., Von Elm, E., Gamble, C., Ghersi, D., Ioannidis, J.P., Simes, J. and Williamson, P.R. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One.* 2008, **3**(8), p.e3081.
6. Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J.J., McNair, A., Prinsen, C.A.C., Schmitt, J., Terwee, C.B. and Young, B. The COMET Handbook: version 1.0. *Trials.* 2017, **18**(Suppl 3), p.280.
7. Nystrom, P.O., Bax, R., Dellinger, E.P., Dominioni, L., Knaus, W.A., Meakins, J.L., Ohmann, C., Solomkin, J.S., Wacha, H. and Wittmann, D.H. Proposed definitions for diagnosis, severity scoring, stratification, and outcome for trials on intraabdominal infection. Joint Working Party of SIS North America and Europe. *World J Surg.* 1990, **14**(2), pp.148-158.
8. *Food and Drug Administeration. Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry.* [Online]. 2018. [Accessed]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm321390.pdf
   ** This is the Food and Drug Administration guidelines which specify the outcomes that should be reported on in complicated intra-abdominal infection trials.
9. *European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. Revision 3 (Draft).* [Online]. 2018. [Accessed July 2019]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf
   ** This document is the guidance provided by the European Medicines Agency for investigators who wish to evaluate new antibiotics for bacterial infections. Within in it, it provides guidance on the appropriate trial design as well as guidance on the outcomes that should be reported on in complicated intra-abdominal infection trials.

10. Evans, S., Rubin, D.B., Powers, J.H. and Follmann, D. Analysis Populations in Anti-Infective Clinical Trials: Whom to Analyze? *Stat Commun Infect Dis.* 2018, **10**(1).
11. Evans, S.R., Rubin, D., Follmann, D., Pennello, G., Huskins, W.C., Powers, J.H., Schoenfeld, D., Chuang-Stein, C., Cosgrove, S.E., Fowler, V.G., Jr., Lautenbach, E. and Chambers, H.F. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). *Clin Infect Dis.* 2015, **61**(5), pp.800-806.
12. Solomkin, J.S. A Cool Reception for Desirability of Outcome Ranking (DOOR)/Response Adjusted for Duration of Antibiotic Risk (RADAR) in Intra-abdominal Infections. *Clin Infect Dis.* 2017, **65**(9), pp.1580-1581.
13. Celestin, A.R., Odom, S.R., Angelidou, K., Evans, S.R., Coimbra, R., Guidry, C.A., Cuschieri, J., Banton, K.L., O'Neill, P.J., Askari, R., Namias, N., Duane, T.M., Claridge, J.A., Dellinger, E.P., Sawyer, R.A. and Cook, C.H. Novel Method Suggests Global Superiority of Short-Duration Antibiotics for Intra-abdominal Infections. *Clin Infect Dis.* 2017, **65**(9), pp.1577-1579.
14. Sawyer, R.G., Claridge, J.A., Nathens, A.B., Rotstein, O.D., Duane, T.M., Evans, H.L., Cook, C.H., O'Neill, P.J., Mazuski, J.E., Askari, R., Wilson, M.A., Napolitano, L.M., Namias, N., Miller, P.R., Dellinger, E.P., Watson, C.M., Coimbra, R., Dent, D.L., Lowry, S.F., Cocanour, C.S., West, M.A., Banton, K.L., Cheadle, W.G., Lipsett, P.A., Guidry, C.A., Popovsky, K. and Investigators, S.-I.T. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med.* 2015, **372**(21), pp.1996-2005.
    ** This landmark randomised controlled trial (RCT) was the first RCT to evaluate antibiotic duration in complicated intra-abdominal infections. This trial showed that short course antibiotics (median 4 days) are as effective as longer courses (median 8 days).
15. Schweitzer, V.A., van Smeden, M., Postma, D.F., Oosterheert, J.J., Bonten, M.J.M. and van Werkhoven, C.H. Response Adjusted for Days of Antibiotic Risk (RADAR): evaluation of a novel method to compare strategies to optimize antibiotic use. *Clin Microbiol Infect.* 2017, **23**(12), pp.980-985.
    * This study was a post hoc analysis, where participants from the CAP-START trial treated with β-lactams and those treated with fluoroquinolones were ranked according to DOOR/RADAR outcomes. This study found that while
16. Solomkin, J., Evans, D., Slepavicius, A., Lee, P., Marsh, A., Tsai, L., Sutcliffe, J.A. and Horn, P. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg.* 2017, **152**(3), pp.224-232.
    * This randomised controlled trial found that eravacycline was non-inferior to ertapenem in the treatment of complicated intra-abdominal infections
17. Solomkin, J.S., Gardovskis, J., Lawrence, K., Montravers, P., Sway, A., Evans, D. and Tsai, L. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs. Meropenem in the Treatment of Complicated Intra-Abdominal Infections. *Clin Infect Dis.* 2018.
    * This randomised controlled trial found that eravacycline was non-inferior to meropenem in the treatment of complicated intra-abdominal infections
18. Qin, X., Tran, B.G., Kim, M.J., Wang, L., Nguyen, D.A., Chen, Q., Song, J., Laud, P.J., Stone, G.G. and Chow, J.W. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. *Int J Antimicrob Agents.* 2017, **49**(5), pp.579-588.
    * This randomised controlled trial demonstrated that cefatzidime/avibactem plus metronidazole was non-inferior to meropenem in the treatment of complicated intra-abdominal infections in adults in Asia
19. Chen, Y., Zhu, D., Zhang, Y., Zhao, Y., Chen, G., Li, P., Xu, L., Yan, P., Hickman, M.A., Xu, X., Tawadrous, M. and Wible, M. A multicenter, double-blind, randomized, comparison study of the efficacy and safety of tigecycline to imipenem/cilastatin to treat complicated intra-

abdominal infections in hospitalized subjects in China. *Ther Clin Risk Manag.* 2018, **14**, pp.2327-2339.

* This randomised controlled trial demonstrated that tigecycline was non-inferior to imipenem in the treatment of complicated intra-abdominal infections

20. Montravers, P., Tubach, F., Lescot, T., Veber, B., Esposito-Farese, M., Seguin, P., Paugam, C., Lepape, A., Meistelman, C., Cousson, J., Tesniere, A., Plantefeve, G., Blasco, G., Asehnoune, K., Jaber, S., Lasocki, S., Dupont, H. and Group, D.T. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. *Intensive Care Med.* 2018, **44**(3), pp.300-310.

** This is the second randomised controlled trial to evaluate antibiotic duration for complicated intra-abdominal infections. This trial showed that short course antibotic therapy reduced antibiotic exposure.