Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis

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Background: In some centers, outpatient management for cancer patients with low-risk febrile neutropenia (FN) has been implemented into routine clinical practice. Our objective was to evaluate the current level of evidence before supporting widespread adoption of outpatient management for this population.

Methods: We systematically reviewed randomized controlled trials evaluating efficacy and safety of outpatient management of FN.

Results: From 1448 reviewed articles, 14 studies were included for meta-analysis. (i) Inpatient versus outpatient setting (6 studies) was not significantly associated with treatment failure (risk ratio 0.81; 95% confidence interval (CI) 0.55–1.19; P = 0.28). Death occurred in 13 of 742 FN episodes with no difference between the two groups (risk ratio 1.11; 95% CI 0.41–3.05; P = 0.83). (ii) Outpatient oral versus outpatient parenteral antibiotics (8 studies) were similarly efficacious with no association between route of drug administration and treatment failure (risk ratio 0.93; 95% CI 0.65–1.32; P = 0.55–1.19).

Conclusion: Based on the current literature, outpatient treatment of FN is a safe and efficacious alternative to inpatient management. Variation between studies in terms of time to discharge, choice of antibiotic class, and age of study population may limit the interpretation of the data.

Key words: ambulatory care, antibacterial-agents, fever, neutropenia, outpatients

Introduction

Febrile neutropenia (FN) remains a frequent complication of chemotherapy for patients with cancer, despite recent advances in infection prevention [1]. For many decades, the standard treatment of FN had been inpatient management with broad-spectrum i.v. antibiotics for all patients [2]. It is now well recognized, however, that patients with FN are a heterogeneous population, with only a small proportion developing a serious medical complication [3]. Consequently, less aggressive treatment approaches, such as p.o. treatment regimens and outpatient management, have been endorsed for FN episodes at low risk for severe infection [4].

Evidence has been established that for adult patients with low-risk FN who are treated entirely as inpatients, combination p.o. antibiotics are equivalent in terms of efficacy and safety to parenteral regimens [5–7]. It is, however, important to note that equivalence of p.o. regimens to i.v. regimens in the inpatient setting does not necessarily imply equivalence in either safety or efficacy of the same regimen in the outpatient setting.

Outpatient strategies may be broadly divided into those in which patients are admitted for a period of hospitalization followed by early discharge, or those in which patients are discharged home the same day following a brief baseline assessment without hospitalization. Outpatient treatment of FN, either early discharge or entirely outpatient management, is attractive for a number of reasons including reduced risk of healthcare-related infection and considerable cost savings, as the major financial burden of conventional FN management is the cost of inpatient care [8].

There is some evidence suggesting that outpatient management in cancer patients with low-risk FN might be a safe alternative to traditional inpatient management [9]. Furthermore, current national and international guidelines have endorsed less aggressive empiric antibiotic strategies, including outpatient and/or p.o. antibiotic regimens, for adult cancer patients with low-risk FN [2, 10, 11]. A recent survey among American physicians revealed that 82% of the respondents use outpatient antibiotics for selected low-risk FN patients, indicating a substantial change in clinical practice over the past few years [12].

Our intention was to evaluate the current level of evidence before supporting widespread adoption of outpatient management for this population. Some uncertainty might emerge due to the considerable variation between conducted studies in terms of time to discharge (immediate versus early discharge after 24–72 h), initial drug administration (p.o. treatment versus sequential i.v.–p.o. treatment), choice of...
antibiotic class, and age of the study population (adults versus children). Nevertheless, we anticipated similar effects of setting and route of antibiotic administration among these subgroups, and therefore, we believed that these studies were combinable for our purpose.

While a recent systematic review compared p.o. versus i.v. treatment of FN, we present the first systematic review and meta-analysis that specifically focused on treatment setting (i.e. inpatient versus outpatient), which is of greater clinical and health resource relevance [6]. Our primary objective was to compare outpatient versus inpatient antibiotic therapy in febrile neutropenic cancer patients. Our secondary objective was to compare p.o. versus i.v. antibiotic therapy in febrile neutropenic cancer patients who are treated in an outpatient setting.

methods
This meta-analysis was carried out according to the recommendations of the PRISMA statement [13].

data sources and searches
We carried out an electronic search of OVID Medline (from 1950 to February 2010), EMBASE (from 1980 to February 2010), and The Cochrane Central Register of Controlled Trials (CENTRAL; until the first quarter of 2010); the search strategy is available as online supplementary data (available at Annals of Oncology online). We also searched relevant references and conference proceedings from 2007 to 2010 using the Web of Science and Scopus databases.

study selection
For the primary objective, we included randomized controlled trials (RCTs) comparing any outpatient antibiotic treatment to any inpatient antibiotic treatment for the management of FN in cancer patients. The outpatient strategy could be initiated at presentation or as part of an early discharge strategy in which all patients were initially treated as inpatients and those allocated to outpatient treatment were switched to outpatient therapy after a predefined time period independent of neutrophil count.

For the secondary objective, we included RCTs comparing any p.o. antibiotics to any i.v. antibiotics, for the outpatient management of FN in cancer patients. The p.o. antibiotics could be initiated at presentation in patients allocated to p.o. treatment or as part of a sequential i.v. to p.o. strategy. In the sequential strategy, all patients were initially treated with i.v. therapy and those allocated to p.o. treatment were switched to p.o. therapy after a predefined time period independent of the neutrophil count.

One reviewer (OT) evaluated the titles and abstracts of publications identified by the search strategy. Any publication thought to be potentially relevant was retrieved in full and evaluated by two reviewers (OT and MCE). Final inclusion of studies in the meta-analysis was determined by agreement of both reviewers. Agreement between reviewers was evaluated by using a kappa statistic [14].

data extraction and quality assessment
Two review authors (OT and MCE) independently extracted data from included trials. Data extraction was carried out using a standardized data collection form.

The primary outcome measure for both objectives was treatment failure at 30 days. Consistent with the literature, treatment failure was defined as a composite end point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; and any addition to, or modification of the assigned intervention, including readmission. Secondary outcome measures were (i) all-cause mortality at 30 days, (ii) adverse events requiring discontinuation/ modification of therapy, and (iii) readmission to the hospital. We carried out subgroup analyses for all outcomes by age (children versus adults) with this categorization being defined by each individual trial.

To assess methodological quality and risk of bias, included articles were examined for (i) sequence generation; (ii) allocation concealment; (iii) blinding; (iv) incomplete outcome data, and (v) intention-to-treat (ITT) analysis.

data synthesis and analysis
This meta-analysis was carried out using Review Manager (RevMan5). We carried out a per protocol (PP) analysis and calculated pooled risk ratios (RR) with 95% confidence intervals for dichotomous data (Mantel–Haenszel method). We also determined absolute risk reductions (ARR) and considered numbers needed to treat (NNT).

Sensitivity analyses were carried out to determine whether conclusions were robust to methodological quality and decisions made during the review process such as combining patient data of entire outpatient and sequential inpatient–outpatient management for the primary objective, combining patient data of entire p.o. therapy and sequential i.v.–p.o. therapy for the secondary objective, or inclusion/exclusion of particular studies. Sensitivity analysis also was conducted by sequence generation and allocation concealment. To further assess the robustness of the findings, we also carried out best–worst case analyses [15].

Because we anticipated heterogeneity between studies, a random effects model was used for all analyses. We also carried out a statistical test for heterogeneity using the Cochran Q test and quantified the degree of heterogeneity with the I² statistic [16]. We considered examination of publication bias using a funnel plot [17].

results
Figure 1 illustrates the flow diagram of trial identification and selection. A total of 1448 titles and abstracts were reviewed, and 21 full articles were retrieved. Of these, six [18–23] and eight [24–31] satisfied eligibility criteria for the primary and secondary objectives, respectively, and were included in the final meta-analysis. The reasons for excluding seven articles were: no outpatient episodes assessed (three articles) [32–34], trial not randomized (three articles) [35–37], and both treatment arms outpatient sequential i.v. to oral treatment (one article) [38]. The reviewers had almost perfect agreement on articles for inclusion, with a kappa statistic of 0.89 [95% confidence intervals (CI) 0.68–1.00].

Clinical characteristics of the 14 included studies are presented in Table 1, which includes six studies related to inpatient versus outpatient management and eight studies related to p.o. versus i.v. antibiotics in the outpatient setting. Seven studies were carried out in each adult and pediatric populations, representing a total of 1677 episodes (ITT). PP analysis was carried out on 1595 episodes (missing data, n = 82). In studies comparing inpatient versus outpatient management, drug administration was i.v. versus i.v. (one adult and two pediatric studies) [18, 22, 23], i.v. versus p.o. (two adult studies) [19, 20], or p.o. versus p.o. (one adult study) [21]. Two of the studies evaluated entire outpatient management (both adult studies) [19, 21], whereas the remaining studies applied an early discharge policy. In studies comparing outpatient i.v. with outpatient p.o. management,
The primary objective (inpatient versus outpatient management) encompassed 363 (inpatient) and 375 (outpatient) episodes of FN. When data from all six studies were synthesized, treatment setting was not significantly associated with treatment failure (risk ratio 0.81; 95% CI 0.55 to 1.19; P = 0.28). Inpatient management was associated with a marginal ARR of 2% for treatment failure (95% CI, −0.06 to 0.02; P = 0.29; NNT = 50). The results are outlined in Figure 2 and Table 2.

The secondary objective (route of drug administration in the outpatient setting) involved 426 (i.v. antibiotics) and 431 (p.o. antibiotics) episodes of FN, respectively, corresponding to a total of eight studies. Figure 3 and Table 2 illustrate that there was no association between route of drug administration and treatment failure (RR 0.93; 95% CI 0.65–1.32; P = 0.67). These results correspond to an absolute risk difference of 2% favoring outpatient i.v. (95% CI −0.08 to 0.04; P = 0.52; NNT = 50).

Table 2 summarizes all outcomes of our analysis. Inpatient treatment did not differ significantly from outpatient care with regard to treatment failure and mortality. Overall mortality in the six studies comparing inpatient and outpatient management was 1.8% (13/742 total; children 5/268 = 1.9%, adults 8/474 = 1.7%), with no difference between the two groups (inpatient 7/365; outpatient 6/377; risk ratio 1.11; 95% CI 0.41 to 3.05; P = 0.83). Data on adverse events requiring discontinuation or modification of therapy were only reported in one study. In studies where all episodes were managed in an outpatient setting, the route of drug administration did not have an impact on treatment failure, adverse events requiring discontinuation or modification of therapy, or readmission; although there was a tendency toward inferiority for p.o. outpatient management in the subgroup of children in terms of readmission (risk ratio 0.52; 95% CI 0.24–1.09; P = 0.08). No patient died in those eight studies (816 episodes). None of the stratified analyses revealed significant differences between adult and pediatric studies (Table 2).

The inclusion of two studies for this meta-analysis was controversial. One trial assessed eligibility for outpatient care after group allocation [18]. The other trial included ‘neutropenic’ patients with an absolute neutrophil count of 300–1000 neutrophils per microliter, whereas all other studies used an absolute neutrophil count of <500 neutrophils per microliter to define neutropenia [25]. As a sensitivity analysis, we repeated data synthesis without those studies; results were qualitatively unchanged (data not shown). Sensitivity analysis was also carried out to analyze the impact of time of discharge (immediate versus early discharge), route of initial drug administration (p.o. versus sequential i.v.–p.o.), allocation generation (adequate versus unclear), and allocation concealment (adequate versus unclear) on treatment failure. The results also were unchanged when data analysis was repeated accordingly (data not shown). Best–worst case analyses revealed the following results: (i) treatment failure (objective 1); best case favoring inpatient management RR 0.60 (95% CI 0.42–0.86), worst case RR 1.24 (95% CI 0.88–1.74); and (ii) treatment failure (objective 2); best case favoring outpatient i.v. RR 0.76 (95% CI 0.52–1.13), worst case RR 1.14 (95% CI 0.78–1.65).

Since both objectives included <10 studies each, tests for funnel plot asymmetry were not carried out [39].

**discussion**

In some centers, outpatient management for cancer patients with low-risk FN has been implemented into routine clinical practice. However, a systematic comparison of efficacy and safety of outpatient strategies in comparison with inpatient strategies had not previously been conducted. Although there have been several narrative reviews of outpatient management of FN [4, 9], our study is important because it is the first study, to our knowledge, to quantitatively synthesize the evidence comparing the two most clinically important management strategies, namely outpatient versus inpatient management. Here, we demonstrate that outpatient treatment is an
<table>
<thead>
<tr>
<th>Group/author</th>
<th>Year</th>
<th>Febrile neutropenia episodes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Discharge&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Inpatient Drug</th>
<th>Treatment duration (days, mean)</th>
<th>Outpatient Drug</th>
<th>Treatment duration (days, mean)</th>
<th>FUO&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>L &amp; L&lt;sup&gt;d&lt;/sup&gt; (%)</th>
<th>ANC &lt;100&lt;sup&gt;e&lt;/sup&gt; (%)</th>
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<tbody>
<tr>
<td>Adults</td>
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<td>i.v. versus i.v.</td>
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<tr>
<td>Rapoport [22]</td>
<td>1999</td>
<td>44/40</td>
<td>After 48–72 h</td>
<td>Ceftriaxone and aminoglycosides</td>
<td>6.3</td>
<td>Ceftriaxone and aminoglycosides</td>
<td>6.0</td>
<td>50</td>
<td>36</td>
<td>36</td>
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<td>i.v. versus p.o.</td>
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<tr>
<td>Innes [20]</td>
<td>2003</td>
<td>67/68</td>
<td>After 24 h</td>
<td>Piperacillin/tazo. and gentamicin</td>
<td>NR</td>
<td>Ciprofloxacin and amoxicillin/clavulanate</td>
<td>NR</td>
<td>37</td>
<td>5</td>
<td>NR</td>
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<tr>
<td>Hidalgo [19]</td>
<td>1999</td>
<td>50/50</td>
<td>Immediate</td>
<td>Ceftriaxone and amikacin</td>
<td>NR</td>
<td>Ofloxacin</td>
<td>NR</td>
<td>68</td>
<td>11</td>
<td>41</td>
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<td>Malik [21]</td>
<td>1995</td>
<td>91/91</td>
<td>Immediate</td>
<td>Ofloxacin</td>
<td>NR</td>
<td>Ofloxacin</td>
<td>NR</td>
<td>71</td>
<td>31</td>
<td>49</td>
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<td>Children</td>
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<td>i.v. versus i.v.</td>
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<tr>
<td>Ahmed [18]</td>
<td>2007</td>
<td>63 / 66</td>
<td>After 72 h</td>
<td>Imipenem</td>
<td>10.4</td>
<td>Ceftriaxone and amikacin</td>
<td>9.4</td>
<td>28</td>
<td>82</td>
<td>57</td>
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<tr>
<td>Santolaya [23]</td>
<td>2004</td>
<td>71/78</td>
<td>After 24–36 h</td>
<td>Ceftriaxone and teicoplanin</td>
<td>6.4</td>
<td>Ceftriaxone and teicoplanin</td>
<td>6.1</td>
<td>38</td>
<td>45</td>
<td>NR</td>
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<td>Adults</td>
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<tr>
<td>Sebban [31]</td>
<td>2008</td>
<td>47/49</td>
<td>After 24–48 h</td>
<td>Ceftriaxone</td>
<td>5&lt;sup&gt;′&lt;/sup&gt;</td>
<td>Moxifloxacin</td>
<td>4&lt;sup&gt;′&lt;/sup&gt;</td>
<td>71</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>Minotti [25]</td>
<td>1999</td>
<td>20/21</td>
<td>Immediate</td>
<td>Ceftriaxone</td>
<td>NR</td>
<td>Ciprofloxacin</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rubenstein [30]</td>
<td>1993</td>
<td>47/49</td>
<td>Immediate</td>
<td>Aztreonam and clindamycin</td>
<td>8&lt;sup&gt;′&lt;/sup&gt;</td>
<td>Ciprofloxacin and clindamycin</td>
<td>7&lt;sup&gt;′&lt;/sup&gt;</td>
<td>61</td>
<td>26</td>
<td>59</td>
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<tr>
<td>Children</td>
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<tr>
<td>Gupta [24]</td>
<td>2009</td>
<td>61/62</td>
<td>Immediate</td>
<td>Ceftriaxone and amikacin</td>
<td>6&lt;sup&gt;′&lt;/sup&gt;</td>
<td>Ofloxacin and amoxicillin/clavulanate</td>
<td>6&lt;sup&gt;′&lt;/sup&gt;</td>
<td>26</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Petrilli [29]</td>
<td>2000</td>
<td>70/68</td>
<td>Immediate</td>
<td>Ceftriaxone</td>
<td>NR</td>
<td>Ciprofloxacin</td>
<td>NR</td>
<td>36</td>
<td>4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>NR</td>
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<tr>
<td>Sequential i.v.-p.o.</td>
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<tr>
<td>Paganini [27]</td>
<td>2003</td>
<td>89/88</td>
<td>Immediate</td>
<td>Ceftriaxone</td>
<td>4.8</td>
<td>Ciprofloxacin</td>
<td>4.5</td>
<td>28</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td>Paganini [28]</td>
<td>2000</td>
<td>80/74</td>
<td>After 72 h</td>
<td>Ceftriaxone and amikacin</td>
<td>7</td>
<td>Cefixime</td>
<td>7</td>
<td>65</td>
<td>57</td>
<td>NR</td>
</tr>
<tr>
<td>Mullen [26]</td>
<td>1999</td>
<td>33/40</td>
<td>Immediate</td>
<td>Ceftriaxone</td>
<td>4.9</td>
<td>Ciprofloxacin</td>
<td>4.6</td>
<td>89</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
<td>60</td>
</tr>
</tbody>
</table>

<sup>a</sup>Absolute number of episodes per randomized group; for example for Innes, 67 episodes were treated as inpatients with i.v. antibiotics and 68 episodes were treated as outpatients with oral antibiotics (all outpatients were discharged after 24 h as displayed in the fourth column).

<sup>b</sup>Only applies to outpatient episodes in the study (objective 1).

<sup>c</sup>Fever of unknown origin defined as no clinical focus with negative microbiological tests.

<sup>d</sup>Percent of leukemia and lymphoma patients in the entire study population.

<sup>e</sup>Percent of patients with absolute neutrophil count <100 per microliter; <sup>1</sup>median, <sup>1</sup>only lymphoma, <sup>1</sup>only leukemia (lymphoma reported together with solid tumors), <sup>1</sup>neutropenia defined as absolute neutrophil count ≥3000/<sub>1000</sub> per microliter.

NR, not reported.
acceptable alternative to inpatient treatment in cancer patients with low-risk FN.

We anticipated similar effects of the included trials before initiating data synthesis. Accordingly, we pooled the weighted estimates of each study. However, the validity of the pooled

Figure 2. Inpatient versus outpatient—Forest plot of treatment failure. Squares to the left of the vertical line indicate a decreased risk of developing treatment failure in patients receiving inpatient management. Horizontal lines through the squares represent 95% confidence intervals (CIs). The diamonds represent the overall risk ratio (RR) from the meta-analyses and the corresponding 95% CIs.

Table 2. Summary of outcomes: inpatient versus outpatient management (primary objective; upper part) and outpatient parenteral antibiotics versus outpatient oral antibiotics (secondary objective; lower part)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (episodes)</th>
<th>Risk ratio (95% CI; P value)</th>
<th>Risk reduction (95% CI; P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient versus outpatient</td>
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<tr>
<td>Failure (PPA)</td>
<td>6 (738)</td>
<td>0.81 (0.55–1.19; 0.28)</td>
<td>−0.02 (−0.06 to 0.02; 0.29)</td>
</tr>
<tr>
<td>Adults</td>
<td>4 (470)</td>
<td>0.79 (0.52–1.20; 0.27)</td>
<td>−0.05 (−0.11 to 0.02; 0.15)</td>
</tr>
<tr>
<td>Children</td>
<td>2 (268)</td>
<td>0.93 (0.32–2.71; 0.89)</td>
<td>0.00 (−0.06 to 0.05; 0.85)</td>
</tr>
<tr>
<td>Mortality</td>
<td>6 (742)</td>
<td>1.11 (0.41–3.05; 0.83)</td>
<td>0.01 (−0.01 to 0.03; 0.54)</td>
</tr>
<tr>
<td>Adults</td>
<td>4 (474)</td>
<td>0.96 (0.27–3.43; 0.95)</td>
<td>0.00 (−0.02 to 0.03; 0.81)</td>
</tr>
<tr>
<td>Children</td>
<td>2 (268)</td>
<td>1.43 (0.27–7.42; 0.67)</td>
<td>0.01 (−0.02 to 0.04; 0.51)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Data only reported in one study</td>
<td></td>
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<tr>
<td>Readmission</td>
<td>Not applicable to this primary objective</td>
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<tr>
<td>Outpatient i.v. versus outpatient p.o.</td>
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<tr>
<td>Failure (PPA)</td>
<td>8 (857)</td>
<td>0.93 (0.65–1.32; 0.67)</td>
<td>−0.02 (−0.08 to 0.04; 0.52)</td>
</tr>
<tr>
<td>Adults</td>
<td>3 (218)</td>
<td>0.95 (0.29–3.13; 0.94)</td>
<td>0.00 (−0.18 to 0.19; 0.97)</td>
</tr>
<tr>
<td>Children</td>
<td>5 (639)</td>
<td>0.90 (0.64–1.26; 0.53)</td>
<td>−0.02 (−0.08 to 0.04; 0.50)</td>
</tr>
<tr>
<td>Mortality</td>
<td>No deaths have been observed in any of the included studies</td>
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<tr>
<td>Toxicity</td>
<td>4 (404)</td>
<td>0.59 (0.06–5.85; 0.65)</td>
<td>−0.03 (−0.07 to 0.02; 0.27)</td>
</tr>
<tr>
<td>Adults</td>
<td>2 (177)</td>
<td>0.72 (0.02–33.74; 0.87)</td>
<td>−0.03 (−0.28 to 0.21; 0.79)</td>
</tr>
<tr>
<td>Children</td>
<td>2 (227)</td>
<td>0.40 (0.02–9.55; 0.57)</td>
<td>−0.02 (−0.06 to 0.02; 0.40)</td>
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<tr>
<td>Readmission</td>
<td>7 (816)</td>
<td>0.62 (0.28–1.39; 0.25)</td>
<td>−0.03 (−0.08 to 0.01; 0.14)</td>
</tr>
<tr>
<td>Adults</td>
<td>2 (177)</td>
<td>0.47 (0.01–14.61; 0.66)</td>
<td>−0.03 (−0.28 to 0.21; 0.79)</td>
</tr>
<tr>
<td>Children</td>
<td>5 (639)</td>
<td>0.52 (0.24–1.09; 0.08)</td>
<td>−0.03 (−0.07 to 0.01; 0.19)</td>
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</table>

CI, confidence interval; PPA, per protocol analysis.
Figure 3. Intravenous versus oral treatment in ambulatory care—Forest plot of treatment failure. Squares to the left of the vertical line indicate a decreased risk in developing treatment failure in patients receiving intravenous antibiotics. Horizontal lines through the squares represent 95% CIs. The diamonds represent the overall risk ratio (RR) from the meta-analyses and the corresponding 95% confidence intervals. p.o. = oral.

In addition to comparing inpatient with outpatient management, we also evaluated whether the route of drug administration in patients that are managed as outpatients has an impact on outcome. Our findings indicate that p.o. antibiotics are equal in terms of efficacy and safety as compared with i.v. administration. This analysis is consistent with post hoc subgroup analyses of a review that compared p.o. versus i.v. antibiotics for FN [6]. These analyses differed as two additional more recently published trials were included in our meta-analysis [24, 31]. There were no deaths within the eight analyzed RCTs further supporting our previous findings (see objective 1) that outpatient strategies are safe alternatives as compared with inpatient treatment.

Available case analysis (PP analysis) was conducted as opposed to ITT analysis. However, we carried out sensitivity analyses (best–worse case analysis) to determine whether conclusions were robust related to this decision. A ‘best case’ scenario favoring inpatient treatment (e.g. all missing data in the inpatient arm were assumed to be success, and all missing data in the outpatient arm were assumed to be treatment failure) would be associated with a significant risk reduction in treatment failure as compared with outpatient treatment. Although this scenario is not realistic, it suggests the possibility that inpatient management may be superior to outpatient management.

Our systematic review has four important limitations. First, further subgroup analyses and meta-regression would have been an optimal approach to better examine potential confounders (e.g. type of underlying disease, severity of neutropenia, or source of infection). However, stratified data were not available to perform additional subgroup analyses, and there were too few studies to consider meta-regression.

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Second, for clinical trials, it is generally preferred to use a primary end point based on a single outcome; however, many of the evaluated studies included multiple outcomes as part of a composite end point ‘treatment failure’. Considering the
limitations of a composite end point, we have assumed that avoiding one outcome has an equal importance as avoiding any other outcome, and that all individual outcome measures are related to the disease process and are equally meaningful. However, this is unlikely the case in the reported studies. In this regard, outpatient failure rates might be overestimated because the composite end point included readmission, and readmission can only happen to patients receiving ambulatory care. However, in the analyzed studies, readmission was consistently associated with persistent fever and/or adverse effects of treatment, both of which would be included as failure in the inpatient arm. Thus, we do not claim that differential susceptibility to failure biased our findings. Third, there is a possibility that some conducted RCTs have not been published. Due to the limited number of included studies, we could not assess funnel plot asymmetry to determine whether publication bias was present. Fourth, uncertainty remains to whether our data can establish definite noninferiority of outpatient therapy. A lack of statistical power to demonstrate superiority of inpatient treatment cannot be excluded.

Our meta-analysis suggests that outpatient treatment of FN is a safe and efficacious alternative to inpatient management. However, there are several important questions that need to be addressed in future research. First, are outpatient strategies feasible in lower income countries? Although 8 of 14 trials analyzed in this review were conducted in lower income countries [18, 21–24, 27–29], the external validity of the findings outside the carefully controlled setting of an RCT remains unclear. Second, is outpatient management feasible in rural areas? Most of the trials conducted so far have excluded patients that live in remote areas. Third, further research is necessary to address the issue of patients’ preferences. If efficacy and safety do not substantially differ between treatment strategies, individual preferences should impact on choosing the appropriate treatment setting and route of drug administration. We suggest that large observational studies from a variety of health settings would substantially add information to answer these questions in the future.

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references


