Benchmarking inappropriate empirical antibiotic treatment

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Abstract

Inappropriate empirical antibiotic treatment for severe infections is associated with increased mortality. Superfluous treatment is associated with resistance induction. We aimed to define acceptable rates of inappropriate empirical antibiotic treatment. We included all prospective cohort studies published between 1975 and 2009 reporting the proportion of appropriate and inappropriate empirical antibiotic treatment of microbiologically documented infections. Studies were identified in PubMed and in reference lists of included studies. Funnel plots were drawn using the proportion of inappropriate empirical treatment as the effect size. A pooled estimate of inappropriate empirical antibiotic treatment was calculated using a β-binomial model. Control limits were calculated with the overdispersion factor technique and 20% winsorized data. Heterogeneity was assessed through subgroup analysis for categorical moderators and meta-regression for continuous variables. Eighty-seven studies, comprising 92 study groups, with 27 628 patients met inclusion criteria. The pooled rate of inappropriate empirical antibiotic treatment was 28.6% (95% CI 25.4–31.8). Funnel plot analysis yielded a dispersed graph with only 37 (40%) studies falling within the control limits. Using the overdispersion factor technique with 20% winsorizing, 79 (86%) studies fell within the control limits. None of the clinical or methodological factors could explain the large heterogeneity observed. The funnel plot presented can be used to benchmark rates of inappropriate empirical antibiotic treatment. Based on the control limits found, at least 500 patients should be evaluated before establishing a local rate. Lower and higher than expected rates might indicate overly aggressive treatment or poor performance, respectively.

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Introduction

Inappropriate antibiotic usage affects both the single patient and the community. From the single patient perspective, inappropriate empirical antibiotic treatment is associated with a significant increase in mortality [1]. From the community perspective, superfluous antibiotic use leads to economic cost and, more importantly, an ecological problem of resistant bacteria induction [2]. Therefore, empirical antibiotic treatment of suspected moderate to severe bacterial infection does not aim at 100% coverage of all possible pathogens, but is an attempt to strike a balance between coverage and the ecological impact of broad-spectrum antibiotics [3]. We aimed to examine whether this balance is uniform in different practices.

We reviewed studies reporting on the rate of inappropriate empirical antibiotic treatment for documented bacterial infections, following a predefined protocol. We performed a meta-analysis of inappropriate empirical treatment rates. Our aim was to define an acceptable range of rates based on currently reported rates and to assess whether there are factors that underlie a justified deviation from the acceptable range. These results can be used to benchmark appropriateness of empirical antibiotic treatment.

Methods

Data sources

We searched PubMed for studies looking at the percentage of empirical antibiotic treatment. Prospective studies (defined as those where at least data collection was performed prospectively) published between 1975 and 2009 were included if addressing adults (≥18 years) with microbiologically documented infections and treatment was selected by clinicians. Studies where treatment was defined by study protocol or those addressing patients treated with specific antibiotics were excluded. The definition of appropriate empirical antibiotic treatment was treatment that was given before the results of the cultures were known and matched the *in vitro* susceptibility of the pathogen. We permitted the inclusion of studies where up to 10% of microbiologically documented infections cannot be tested *in vitro*; in these cases the study definitions for appropriateness were accepted. We excluded studies assessing meningitis, endocarditis or viral infections; and studies that recruited <50 patients or were published in languages other than English. We used the following search clause: ((antibiot* OR antimicrob* OR anti-bacter* OR antibacter*) AND (approp* OR inapprop* OR adequate OR inadequate)) AND ((cohort* OR prospect*) NOT retrospect*) NOT Review[ptyp] AND 'adult'[MeSH Terms]. References from identified studies were also scanned.

Data extraction

Two reviewers independently extracted the data from included studies. In case of any disagreement between the two reviewers, a third reviewer extracted the data and consensus was reached. We extracted data on appropriate empirical treatment (definition, timing of treatment, number of appropriate and/or inappropriate treated patients). In addition, we extracted data on study characteristics to allow the examination of factors affecting the rate of inappropriate empirical antibiotic treatment. We collected data on settings, study years, study objectives, follow-up duration, patient characteristics, pathogens and source of infection. In cases where data were published in multiple studies, the data were included only once.

Data synthesis and analysis

The pooled estimate of inappropriate empirical antibiotic treatment was calculated using various methods, including fixed and random effects models, simple binomial model and β-binomial model. Fixed and random effects models were performed using COMPREHENSIVE META ANALYSIS version 2.2, Simple binomial and β-binomial calculations were performed using SAS software and SAS BETABIN MACRO (http://www.qistats.co.uk/BetaBinomial.html). Funnel plots were drawn using the proportion of inappropriate empirical treatment as the effect size. The funnel plot graph uses five lines. The central horizontal line is the pooled proportion estimate. The selected model for the pooled proportion estimate was the β-binomial model. This model is proposed for combining overdispersed binomial data across multiple, heterogeneous studies [4]. The upper and lower lines present the control limits, calculated as 2 SD and 3 SD (~95% and ~99.8% prediction limits). Control limits are calculated using the overdispersion factor technique and 20% winsorized data [5]. Any point falling outside the control limits is an outlier, suggesting a special cause for the variation. The funnel plots were prepared based on a funnel plot EXCEL template downloaded from Easter Region Public Health Observatory (ERPHO, http://www.erpho.org.uk/).

Analysing the cause for variation of the effect size used subgroup analysis for categorical moderators and meta-regression for continuous variables (Comprehensive Meta-analysis Version 2, Biostat, Englewood, NJ, USA (2005)). Correlation analysis between variables was performed using SPSS (version PASW STATISTICS 17.0, Release 17.0.2, SPSS Inc., Chicago, IL, USA).

Results

The search for potentially eligible studies yielded 1053 references. Eighty-seven studies reporting rate of inappropriate empirical treatment and meeting the inclusion criteria were included (Fig. 1). These publications comprised 92 study

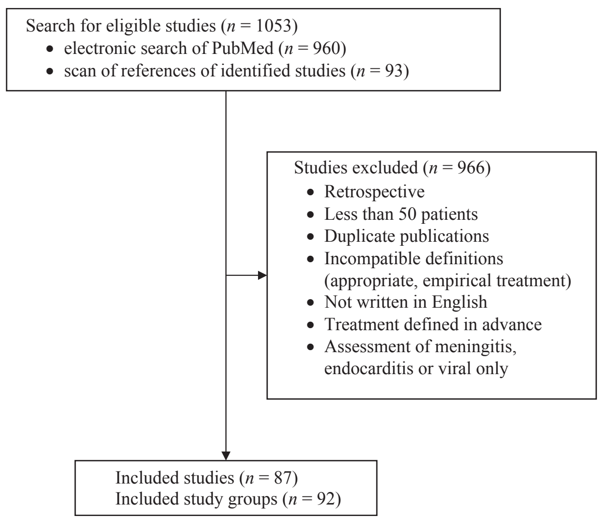

FIG. 1. Study flow.

TABLE 1. Pooled rates of inappropriate empirical antibiotic treatment

Method	Estimate (%)	Lower 95% CI	Upper 95% CI
Simple binomial	29.19	28.65	29.72
β-Binomial	28.65	25.45	31.85
Meta-analysis (fixed)	31.4	30.8	32
Meta-analysis (random)	26.3	23.7	29