A breach in patients’ safety in randomized controlled trials of antibiotic drugs

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In a number of randomized controlled trials of antibiotic drugs the pathogens cultured from patients and their in vitro susceptibilities to the study drugs were not disclosed to the physicians during the whole course of the disease. These trials included patients with sepsis and bacteraemia. In clinical practice the information on the pathogen and its susceptibilities serves to re-evaluate the antibiotic treatment on the second or third day. As there is strong evidence that antibiotic treatment (empirical and definitive) matching the in vitro susceptibility of the pathogen reduces fatality rates in severe infections, withholding these data is a breach in patient safety. Sponsors and investigators of clinical trials of antibiotic drugs should ensure that the susceptibility of pathogens to the trial drugs are made available to clinicians in real time and taken into account when considering change in patient management, as would be the case in routine clinical practice. Members of research ethics committees should make sure that the protocols provide for this, while journals considering publication of clinical trial results should ask that details on the availability of susceptibilities to the trial antibiotics are disclosed in the methods section.

Keywords: in vitro susceptibility, survival, ethics

We recently read the protocol of an ongoing, Phase III, multicentre and multinational randomized controlled trial of a new antibiotic in patients with complicated urinary tract infection. Septic patients, patients with bacteraemia and patients with pyelonephritis were included in the study. According to the study protocol, the in vitro susceptibilities of the pathogens to the new antibiotic were not tested locally and the susceptibility of the pathogens (whether grown from urine or blood) were unknown to the clinicians during the whole course of the disease. In some locations, testing of susceptibility to the comparator antibiotic was not performed either. Clinicians were expected to change treatment only according to the clinical response.

In clinical practice, patients with severe infections should be re-evaluated on the second or third day after commencement of treatment with regard to clinical improvement, identification of any pathogens grown from cultures and their pattern of antibiotic susceptibility. There is strong evidence that antibiotic treatment (empirical and definitive) matching the in vitro susceptibility of the pathogen reduces the fatality rate in severe infections, regardless of the clinical course in the first days.1–4 In patients with hypotension, the time to initiation of antibiotic treatment that matches the in vitro susceptibility of the pathogen was the most important determinant of survival.5 Dryden et al.5 stress ‘the importance of formally reviewing antibiotic therapy at 48 h, based on the patient’s clinical response and the availability of microbiology test results’. A practice (in clinical trials) that ignores the susceptibilities of pathogens is a breach of patients’ safety.

We wanted to verify whether this specific trial was an exception. We looked for randomized controlled trials of antibiotic drugs that included septic patients and were published in the last 5 years (PubMed search done in December 2012). We found 69 such trials (a list is provided in Table S1, available as Supplementary data at JAC Online). In 18 articles (26%) the authors reported that the susceptibilities of pathogens to the study drugs were available to the clinicians in real time. We wrote to the corresponding authors of the other 51 articles. Twenty-seven responded; one author wrote that he could not divulge the information. Overall, we have information on 44 studies. In 10 studies, susceptibilities of the pathogens were unavailable to clinicians in real time (14% of all trials; 23% of the trials for which we have information).

The source of funding was disclosed in the article or obtained from the author in 53 studies. Out of the 9 studies in which we knew the sponsor and antibiotic susceptibilities were unavailable to the clinicians, 8 (89%) were funded by the pharmaceutical industry, compared with 16/26 (62%) studies in which susceptibilities were available to the clinician. Out of the 18 studies in which we knew the sponsor but were uncertain whether susceptibilities were provided to the clinicians in real time, 16 (89%) were funded by the pharmaceutical industry. We can assume that in some of these 18 studies information on susceptibility was unavailable to the physicians.

Disclosure of antibiotic susceptibilities would not compromise scientific validity of the trials. A mechanism could be found to do it even in double-blinded trials [out of the 35 studies in which

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information was provided, 10 (29%) were double-blinded. It might increase the percentage of failures (on intent-to-treat analysis) or decrease the number of observations that can be included in a per-protocol analysis, and thus increase the sample size needed and the cost of the trial. However, the Declaration of Helsinki clearly states: ‘In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.’\(^7\)

We urge the sponsors and investigators of clinical trials of antibiotic drugs to stop this breach of patients’ safety. They should ensure that the susceptibilities of pathogens to the trial drugs are made available to clinicians in real time, as would be the case in routine clinical practice, and taken into account when considering change in management. Mechanisms can be found to do this in blinded studies. Members of research ethics committees should make sure that the protocols provide for this. Journals should ask that details on the availability of susceptibilities to the trial antibiotics are disclosed in the methods section.

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**Transparency declarations**

None to declare.

### Supplementary data

Table S1 is available as Supplementary data at JAC Online (http://jac.oxford-journals.org/).

### References