Dear Editors:

I read an interesting article titled “Low lymphocyte proportion in bronchoalveolar lavage fluid as a risk factor associated with the change from trimethoprim/sulfamethoxazole used as first-line treatment for Pneumocystis jirovecii pneumonia” by Kim et al. published in the recent issue of Infection & Chemotherapy [1]. In fact, treatment failures or adverse drug reactions (ADRs) that require treatment modification are important issues encountered frequently during the treatment of P. jirovecii pneumonia (PCP), which could result in mortality. The authors investigated 101 patients with PCP, and as described in the article title, they concluded that an initial low lymphocyte proportion (≤45%) in bronchoalveolar lavage fluid (BALF) was an independent risk factor of trimethoprim/sulfamethoxazole (TMP/SMX)-related treatment failure or ADRs and requires change in treatment. According to the results, the authors suggested that physicians could carefully manage PCP patients based on BALF results.

However, I have several concerns regarding the application of these results in actual practice. First, as the authors admitted in the discussion section, treatment failure and ADRs are different end-points i.e., treatment failure could be more attributable to disease severity while ADRs could be more related to host factors. In fact, the percentage of initial severe hypoxemia in patients experiencing treatment failure or ADRs (69%) was considerably different from that observed in the treatment failure group excluding ADRs (88%; the published value of 57.7% must be a typographical error). The mean age of patients experiencing treatment failure or...
ADRs (49 years) was also different from that of patients in the treatment failure group excluding ADRs (59 years). These data suggest that authors should have performed separate analysis for different outcomes. Although the authors mentioned that they performed subgroup analysis (the term of ‘sensitivity analysis’ is probably a typographical error; ‘sensitivity analysis’ would be more adequate) of the risk factors associated with treatment failure, BALF lymphocyte was still significant. It was not clear how they controlled for disease severity as disease severity should be a very important determinant of treatment success or failure. As shown in Kim T et al, 88% (the published value of 57.7% must be a typographical error as mentioned above) of patients in the treatment failure group had severe hypoxemia and more than a quarter of patients in this group needed vasopressor support (both $P$-values were 0.01). The paradoxical result that early treatment resulted in worse outcomes (the odds ratio of time to treatment from onset of symptoms ≤3 days was 4.51 [95% confidence interval, 1.10–18.53]) implies that the patients in the treatment failure group had severe disease at baseline. If the authors performed a separate analysis that focused on treatment failure while controlling for disease severity, a change in the results might be observed. In addition, a simple adjustment of covariates is not sufficient to answer this question. Second, as the authors described in the Discussion section, particulars regarding the conclusion of treatment failure and ADRs and the requirement for drug modification are not clear due to the retrospective nature of this study. In fact, although treatment failure was defined as “clinical deterioration during the first 5 days of therapy or lack of improvement after 7 or more days of treatment” [2], this study did not mention when the treatment failure or ADRs-related treatment modifications occurred. Third, there was a lack of description of co-existing diseases that could affect the treatment outcome. For example, radiological findings only included consolidation and pleural effusion. The most common radiological finding of PCP is neither consolidation nor effusion but ground glass opacity on computed tomography scans [3], which is observed with infectious as well as non-infectious diseases. More than one fifth of the cases in this study involved patients with coexisting cytomegalovirus (CMV) infection; however, there was no mention of how the CMV titer in BALF was measured and how many patients were treated with anti-CMV drugs. Fourth, the cut-point of 45% for proportion of BALF lymphocytes seems arbitrary. In this study, the median percentage of BALF lymphocytes was 47% (only 2% higher than the cut-point) in the treatment success group. This means that many patients who can be successfully treated can be included in the “group at risk of treatment failure” because they showed a BALF lymphocyte proportion below 45% at baseline. The authors have described the results of a previous study conducted in the same institute in the discussion section as “both BAL lymphocyte percentage (2.2% [interquartile range (IQR), 8–45%] vs. 40% [IQR, 29–37%]; $P = 0.005$) ... were lower in patients who showed TMP/SMX treatment failure or ADRs.” The median percentage of BALF lymphocyte was only 40% in the treatment success group, which is even lower than the cut-point of 45%. Can the cut-point of 45% work as a predictor in actual clinical settings?

This study has surely raised important issues; however, further well-designed studies are needed for application to real practice.

REFERENCES


https://icjournal.org
https://doi.org/10.3947/ic.2018.50.3.263