Penicillin binding proteins (PBPs) are involved in the construction of peptidoglycan, which is the major constituent of bacterial cell walls, and the target of β-lactam antibiotics. There is little published research analysing the relationship between β-lactams and differing bacterial PBP targets, and how they can be manipulated in combinations with respect to clinical or microbiological outcomes (i.e. does expanded PBP activity via a combination lead to better in-vitro/in-vivo outcomes).

**RESULTS**

Overall, 86/630 (14%) of all combinations tested showed synergy (Fig. 3.1) and 408/630 (65%) were additive (Fig. 3.2). 136/630 (21%) combinations showed indifference (Fig. 3.3). See also Fig. 4. Tables 2.1-2 show full results for isolates 1 & 2.

Of the 86 'bug-drug' combinations that showed synergy, 42/86 (49%) included Ceftazidime/Aztreonam, representing 42/126 (33%) of all Ceftazidime/Aztreonam based combinations tested. Synergy was most commonly detected in ESBL producers (58/86; 67% of synergistic combinations) and less frequently in the CPE (2/86; 2% of synergistic combinations) and fully sensitive isolates (8/86; 9% of synergistic combinations).

Additive effects were seen in 92/180 (51%) combinations versus ESBLs, compared to 18/90 (20%) in CPEs and 154/180 (86%) in fully sensitive isolates. No antagonism was identified with any antibiotic combination.

**CONCLUSION**

In the combinations tested, synergy or additive effects were common (78%); similar to our previous work with Fosfomycin/β-Lactam combinations (89%), but higher than with Fosfomycin/Non-β-Lactam combinations (28%). The presence of PBP target expansion was similar in synergistic versus additive versus indifferent combinations (58%, 56% and 63%, respectively). Synergy was more common in ESBL-producing E. coli versus fully sensitive and CPE isolates.

Most of the synergistic 'bug-drug' combinations identified contained a BLI. This provisionally suggests BLI may play a key role in synergy. Confirmation using an alternative method and mechanistic elucidation is required. The clinical and microbiological importance of such effects remains unclear.

**REFERENCES**