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**Title:** Effect of I:E ratio on delivery of colistimethate sodium from breath-enhanced and breath-activated nebulizers

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**Body:** Drug delivery via a nebulizer differs depending on the nebulizer/compressor combination and the principle of operation of the nebulizer. Consequently, while breathing patterns (BPs) with different inhalation:exhalation (I:E) ratios can affect delivered dose (DD), this effect differs depending upon the principle of operation. An in vitro investigation into the effect of different I:E ratios on the dose of colistimethate sodium (CMS) delivered via nebulizers was undertaken. Here, results from the breath-activated I-neb AAD System (I-neb) and 2 breath-enhanced nebulizers with TurboBoy SX compressors, the LC Sprint (LCS) and the LC Plus (LCP), are compared. Each nebulizer (n=3, run in triplicate) was loaded with CMS 1 MIU (reconstituted in water, I-neb=1 mL; LCS/LCP=3 mL). Nebulizers were attached to a breathing simulator and run until sputter +60 s with 4 different BPs. Dose delivered to a filter with each BP was analyzed by bioassay.

Table 1: % DD, compared with the 1:1 I:E ratio, for each nebulizer with each BP.

Breathing pattern	I-neb	LCS	LCP
A (I:E ratio 1:1, PIF 23.1 L/min, 15 BPM)	100%	100%	100%
B (I:E ratio 1:2, PIF 23.1 L/min, 10 BPM)	92.3%	83.5%	71.1%
C (I:E ratio 1:3, PIF 21.5 L/min, 7 BPM)	86.9%	68.5%	55.3%
D (I:E ratio 1:4, PIF 23.1 L/min, 6 BPM)	109.4%	59.6%	53.4%

PIF=peak inspiratory flow; BPM=breaths per minute.

Dose delivered via LCS and LCP was proportional to the duration of inhalation. In contrast, a relatively consistent dose was delivered by I-neb, regardless of BP. Aspects of BP, including I:E ratio, may be influenced by pathophysiology; independence of DD from BP is therefore likely to minimize dose variability in the clinical setting.