Cystic fibrosis in the modern therapeutic era: give the shower a think!

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Cystic fibrosis (CF) is a genetic disease whose prognosis has been greatly modified, with a considerable increase in life expectancy over the last 50 years [1]. Several factors may explain this such as follow-up of patients in CF centers applying international recommendations for the best CF care, organ transplantation which is nowadays considered as a routine procedure in the CF therapeutic scheme, newborn screening allowing early management and preventing the delay in diagnosis that has affected many families in areas lacking such screening, and availability of CFTR modulators treatments which restore, at least partially, the CFTR protein activity in some specific genetic indications, other modulators being waited for soon [2,3] ... At the same time, CF patients continue to receive numerous daily treatments such as chest physiotherapy, pancreatic extracts, nebulizations, and others. Great progress has also been made in alleviating everyday life through reducing the mean 2 hours spent per day for therapy [4]. For instance, concerning inhaled therapies, which represent 25-50% of total home time of care [5], the time-consuming nebulization may be replaced by a dry powder inhalation for some antibiotics or may be delivered by more sophisticated devices, such as vibrating-mesh nebulizers, with shorter nebulization duration. Of course the daily use of such electronic nebulizers needs careful maintenance as therapeutic efficiency is closely linked to the mesh performance, which may be altered by mesh plugging over time [6]. Unfortunately, in a recent study performed in 92 CF patients equipped with an e-Flow rapid® nebulizer (58.7% children; mean 1.8 nebulizations per day) [5], we have shown that mesh maintenance was not adequate, with only 39% of the patients using the specific cleaning system of the mesh, the so-called MeshCare®, which consists of a reverse rinse of the mesh by means of a small shower, thus removing the plugs formed by drug deposition into the mesh holes.

We asked these patients to note daily, for 6 months, their number of nebulizations, the kind of nebulized drug, the application of the maintenance procedure, the occurrence and type of nebulizer incidents. At 6 months, their e-Flow rapid® meshes were collected for *in vitro*

characterization of the delivery of 300 mg tobramycin (Tobi®, Novartis), before and after MeshCare® use (5 ml isotonic saline during 20 min). As only 52 patients completed the 6 months data collection, only 52 meshes were tested with a laser diffractometer (Spraytec®, 15 Lpm aspiration; Malvern, UK). They were characterized, as well as 3 brand new meshes, for residual volume, nebulized volume, nebulization duration (until the bip of end or the aerosol production end), aerosol output, MMAD, and particles < 5 µm. A mesh was considered as "out of order" when producing no aerosol and as "defective" when the variation of the nebulized volume was ≥ 15% in comparison with that obtained with a new mesh [7] (Table 1). Three meshes were out of order (5.7%). Mesh properties were clearly altered compared to those of new meshes, with a high variability for all results. Thirty meshes among 49 (61.2%) were defective, 20 generating a too low nebulized volume. No relation was found with the drug used during 6 months (mucoregulators 52%, antibiotics 42%, both 6%), the number of daily nebulizations, and the frequency and kind of nebulizer maintenance. The MeshCare® permitted to statistically improve nearly all tobramycin nebulization parameters, 14 defective meshes (46.6% of the defective meshes) being anew in the expected range of nebulized volume.

Our results consolidate those of a previous work [8] where *in vitro* evaluation of 15 e-Flow®rapid nebulizers used by CF patients for 3 inhaled tobramycin cycles has showed an increase of the mean nebulization duration from 6.7 to 9.8 min in 6 months, a 36% decrease of the aerosol output, with a total of 8 nebulizers switching off prematurely. After replacing a polluted mesh by a new one, parameters are restored to original values. In our study, after 6 months of daily home use, about 7 meshes out of 10 do not deliver a "clinically validated" amount of tobramycin and may compromise the therapeutic efficiency. Contrary to common ideas [5,8-10], no specific factor correlated with mesh dysfunction, and the mere use of the device alters the mesh performance over time. So, in the absence of key factors predictive of

mesh dysfunction and in agreement with the manufacturer's recommendation, we advise a monthly control at home of the nebulization duration with 2.5 ml isotonic saline, and employing the MeshCare® when this duration is increased. We clearly prove for the first time the benefits of this recommendation, allowing the best drug delivery to CF patients. In summary, a mere shower, even in the CF modern therapeutic era, may be sometimes of great help...

Table 1: *In vitro* characteristics of a tobramycin nebulization performed with 3 new meshes and 52 meshes of e-Flow rapid® used for 6 months by cystic fibrosis patients at baseline and after the use of a cleaning system back rinsing the mesh (MeshCare®).

	New meshes (n=3)		Six months used meshes (n=49/52; 3 out of order)	Meshes after back rinsing (n=49/52; 3 out of order)	Mann-Whitney test comparing used to back rinsed meshes
Residual volume (ml)	1.5 ± 0.2 [1.3-1.7]		2.4 ± 0.9 [1.1-4.7]	1.9 ± 0.8 [0.9-4.1]	p=0.0011
Nebulized volume (ml)	3.8 ± 0.3 [3.5-4.6]		2.8 ± 0.9 [0.6-4.2]	3.3 ± 0.8 [1.1-4.2]	p=0.0017
Nebulization duration (min)	8.1 ± 0.7 [7.33-8.66]		9.5 ± 1.1 [5.5-10.0]	8.9 ± 1.5 [5.16-10.0]	p=0.02
Aerosol output (ml/min)	0.47 ± 0.01 [0.46-0.48)		0.31 ± 0.14 [0.06-0.71]	0.39 ± 0.15 [0.11-0.74]	p=0.0018
MMAD (µm)	4.1 ± 0.1 [4.0-4.2]		3.6 ± 0.3 [2.7-4]	3.8 ± 0.3 [2.9-4.5]	p=0.0007
Particles < 5 µm (%)	66 ± 3 [64-69]		76 ± 6 [68-93]	75 ± 7 [60-92]	NS
Defective meshes* (n)	0		30 (61.2%)	16 (32.6%)	-

* A mesh was considered as defective when the variation of the nebulized volume was ≥ 15% in comparison with that obtained with a new mesh

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