PULMONARY ARTERIOVENOUS MALFORMATIONS IN CHILDREN: OUTCOMES OF TRANSCATHETER EMBOLOTHERAPY

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Objective To describe outcomes of transcatheter embolotherapy (TCE) in children with pulmonary arteriovenous malformations (PAVMs).

Study design Chart and imaging review of all children (age ≤18 years) treated for PAVMs by TCE at three hereditary hemorrhagic telangiectasia centers.

Results All 42 treated patients were included, with a mean age of 12 years (range, 4 to 18). Cyanosis was present in 25 of 42 patients (60%). Hemoptysis had occurred in 3 of 42 patients (7%) and neurologic complications (stroke, cerebral abscess) occurred in 8 patients (19%) before assessment. PAVMs were focal in 30 of 42 (71%) and diffuse in 12 of 42 (29%) patients. TCE was performed for 172 PAVMs and 35 diffuse regions (regional TCE). Follow-up was obtained in 38 of 42 (90%) patients (mean, 7 years). After TCE in patients with focal PAVMs, oxygenation improved significantly, with no further complications from the PAVMs. Reperfusion was noted in 23 of 153 (15%) PAVMs. Eighteen of 23 (78 %) of these were retreated, with documented aneurysmal involution in 10 of 13 (77%) patients. TCE complications included pleuritic chest pain (24% of sessions) and deployment complications (device paradoxical embolization or device misplacement) (3% of sessions, 1% of PAVMs), with no long-term complications.

Conclusions PAVMs cause life-threatening complications in children; treatment with TCE is safe, with complication rates comparable to adult rates. *(J Pediatr 2004;145:826-31)*

Pulmonary arteriovenous malformations (PAVMs), are present in at least 30% of adults with hereditary hemorrhagic telangiectasia (HHT),[1] and they have been well characterized.[2-5] Patients with PAVMs are frequently asymptomatic; therefore PAVMs often remain unrecognized until a serious complication develops, such as stroke or cerebral abscess. Neurologic complications occur in approximately 40% of adults with untreated PAVMs and hemorrhagic complications (massive hemoptysis or spontaneous hemothorax) occur in approximately 15%.[2-5] Fortunately, sensitive screening methods have been described,[1] and therapy exists that is both safe and effective. The treatment of choice for PAVMs in adults is transcatheter embolotherapy (TCE).[2,4,6,7]

Only case reports and small case series of up to 5 patients describe the clinical presentation of PAVMs in children, and few report any treatment or outcomes. To date, only 6 case reports of TCE in 8 children[4,8-12] have been published. Five of the 8 reported good results; no follow-up was reported for the other 3 cases.

HHT is increasingly recognized in adults in whom screening and treatment for PAVMs has become the standard of care. Genetic diagnosis has recently become available; therefore we expect increasing numbers of asymptomatic children to be diagnosed with HHT, many of whom will be diagnosed with asymptomatic PAVMs. The clinical presentation of PAVMs and the safety and effectiveness of TCE must therefore be evaluated specifically in children to clarify the role of screening and treatment for PAVMs in children of HHT families.

CP	Collateral perfusion	TCE	Transcatheter embolotherapy
HHT	Hereditary hemorrhagic telangiectasia	SpO₂	Oxygen saturation by pulse oximetry
PAVMs	Pulmonary arteriovenous malformations		

We report the first large series of children with PAVMs describing clinical presentation and outcomes of TCE, with a mean follow-up of 7 years.

METHODS

Subject Selection

From the databases of 617 consecutive patients with PAVMs treated at Yale University (1988 to 2002), Johns Hopkins (1978 to 1988), and University of Toronto (1990 to 2002) HHT Centers, all 42 subjects ≤18 years of age who had undergone TCE for PAVMs were selected. Four included patients (diffuse patients 7, 8, 10, and 12) have been previously reported.[13] Patients were referred to the HHT Centers either for suspected PAVMs or screening in asymptomatic children of HHT families, and investigators kept consecutive lists of treated patients (for John Hopkins and Yale) or a patient database (for University of Toronto).

Medical and radiographic charts were reviewed for collection of the following data: sex, age, symptoms and signs of PAVMs (dyspnea on exertion/exercise intolerance, cyanosis, clubbing), previous complications of PAVMs (stroke, transient ischemic attack, cerebral abscess, massive hemoptysis, spontaneous hemothorax), pulse oximetry (SpO_2), number/type/location of treated PAVMs, complications of TCE, long-term results of TCE (on CT and/or angiography), and follow-up symptoms/complications of PAVMs. Institutional review board approval was obtained from each hospital, except for the Johns Hopkins data, which had been collected by one investigator during the period of 1978 to 1988.

Angiographic Classification

All patients underwent standard diagnostic pulmonary angiography. PAVMs were classified as diffuse or focal through the use of previously defined criteria (diffuse PAVMs were PAVMs involving every segmental artery in at least one lobe).[8] Focal PAVMs were further classified as simple or complex.[9] Simple PAVMs have single or multiple feeding arteries, all originating from one segmental artery. Complex PAVMs have multiple feeding arteries, arising from at least two different segmental arteries.

Treatment

All patients underwent TCE of arteries (diameter ≥ 3 mm) feeding PAVMs, with the use of standard embolic materials (stainless steel coils, platinum coils, detachable balloons, or a combination of these).[10] In several patients it was elected to embolize the feeding artery of a diffusely involved region (regional TCE) from distal to proximal in a segmental artery or subsegmental artery. TCE technique in adults has been described in detail[6,11-13] and was followed in this series with two modifications. First, general anesthesia or heavy sedation was used for all children <12 years old, and, second, diagnostic angiography and TCE were performed on the same day. Completion angiography was performed to assess occlusion of PAVMs immediately after TCE, provided contrast media limits had not been exceeded (5 mL/kg). SpO_2 was measured before TCE and within 24 hours after TCE.

Patients were advised to receive antibiotic prophylaxis for bacteremic procedures to prevent cerebral abscess, even after PAVMs were treated.

Follow-Up

Follow-up assessment occurred annually or biannually after TCE. This included helical CT of the thorax (without contrast in most cases, to avoid risk of air embolism possible with any intravenous injection in patients with PAVMs) and assessment for all known complications of PAVMs and TCE. Based on CT appearance, PAVMs were classified as involuted (Figure) or reperfused.[2,4] Involution was defined as thrombosis, retraction, and scarring of the venous sac connecting the feeding artery to the draining vein. When reperfusion was suspected, pulmonary angiography was performed.

Reperfusion of PAVMs after TCE

As previously defined,[4] reperfused PAVMs were classified as reperfused as the result of recanalization of the occluded artery to the PAVM (either by perfusion through the coils or early deflation of a balloon, after initial successful occlusion of the artery) or reperfusion as the result of a missed accessory feeding artery (accessory feeding artery arising more proximally from the same segmental artery or from another segmental artery but not noted at the time of initial angiography). We have included a third cause for lack of venous sac involution, which we named collateral perfusion (CP), where tiny (1-mm) collateral vessels developed between the feeding artery and the venous sac of the treated PAVM (Figure).

Statistical Methods

Paired t tests were used for comparison of means for SpO_2 before and after TCE. Two-sample comparison of proportions was used for comparison of symptoms/signs in patients with diffuse versus focal PAVMs. All analyses were performed with the use of STATA software.

RESULTS

Baseline Characteristics and Clinical Presentation

All 42 patients meeting inclusion criteria were included. PAVMs were focal in 30 of 42 (71%) patients and diffuse in 12 of 42 (29%); 24 of 42 (57%) reported dyspnea on exertion or exercise intolerance (Table I). Three of 42 (7%) reported previous hemoptysis (minor), and none had previous spontaneous hemothorax. Cyanosis was present in 25 of 42 (60%) and clubbing was present in 19 of 42 (45%). Neurologic complications of PAVMs (transient ischemic attack, MRI-detected stroke, and cerebral abscess) occurred in 8 of 42 (19%). Seven of 8 patients (88%) with previous neurologic complication were cyanotic. The one exception, focal patient 4, had a "silent infarct" noted on MRI. Although the clinical presentation appeared to be more severe in the diffuse group (Table I), neurologic complications occurred in both groups.
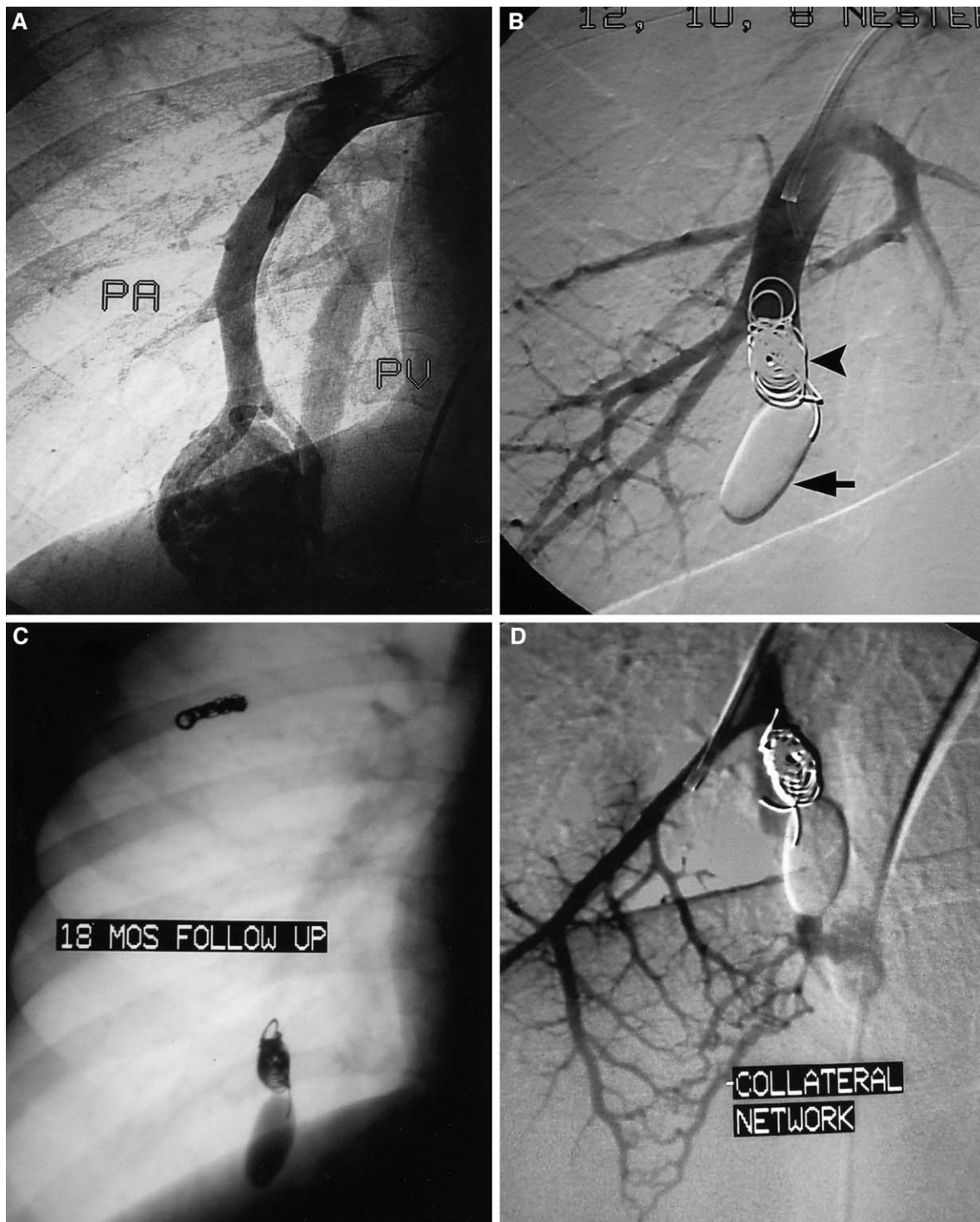
Figure. A, Right pulmonary angiogram in focal patient 24 demonstrates large pulmonary artery branch *(PA)* filling venous sac and draining vein *(PV)*. **B,** Digital subtraction angiogram immediately after treatment demonstrates double occlusion with a detachable balloon *(arrow)* and coils *(arrowhead)*. **C,** Chest radiograph after 18 months' follow-up demonstrates that coils and balloon are intact and coils are present in a second PAVM (superior to first PAVM). **D,** Digital subtraction angiogram of the pulmonary artery branch originally occluded demonstrates a tiny collateral network filling a small residual venous sac.

Ten patients had undergone TCE or surgical resection before referral to our centers (Tables II and III available online at www.us.elsevierhealth.com/jpeds). The outcomes of these procedures were not analyzed. HHT was diagnosed, using clinical criteria[13] in 36 of 42 (86%) of patients.

Angiographic Characteristics and TCE

TCE was performed in all patients, for 172 PAVMs in 76 sessions (Tables II and III). In the focal group, 30 patients had a total of 85 PAVMs that were treated with TCE. Eighteen of 30 (60%) had multiple PAVMs, 66 of 85 PAVMs

(78%) were simple, 19 of 85 (22%) were complex, and 62 of 85 (73%) were located in the lower lobes. In the diffuse group, all 12 patients had innumerable PAVMs, including 87 focal PAVMs treated with TCE and 35 diffusely involved regions treated with regional TCE (see Methods). Some sessions required multiple procedures over a period of several months.

Outcomes of TCE

Follow-up was obtained in 38 of 42 (90%) patients, with mean follow-up of 7 years (range, 1 to 18 years), representing 153 of 172 (89%) PAVMs and 22 of 35 (63%) diffuse regions treated with regional TCE.

Oxygenation Data

In the diffuse group, SpO_2 (pulse oximetry) was available before and after TCE for 26 of 28 sessions (93%). Mean SpO_2 was 83% before TCE (SD = 8.2%; range, 62% to 96%), compared with 88% after TCE (SD = 7.1%; range, 74% to 97%; P = .003). In the focal group, SpO_2 was available before and after TCE for 42 of 48 sessions (88%). Mean SpO_2 was 88% before TCE (SD = 9.4%; range, 44% to 100%), compared with 97% after TCE (SD = 4.5%; range, 72% to 100%; P < .0001). Mean SpO_2 before TCE was significantly lower in the diffuse group (83%) than in the focal group (88%) (P = .02).

Imaging Follow-Up

During the follow-up period, reperfusion of PAVMs was noted on CT scan in 23 of 153 PAVMs (15%), 0 of 22 regions (0%), representing 17 of 38 (45%) patients (Tables II and III); 18 of 23 PAVMs in 13 patients were retreated with TCE with documented involution of the venous sac on follow-up CT in 10 of 13 patients. Reperfusion type was a missed accessory feeding artery in 8 of 23 (35%), recanalization in 11 of 23 (48%), and CP in 12 of 23 (52%). In 6 of 23 (26%) PAVMs, more than one reperfusion type was present (included in totals). In 4 patients, a total of 6 PAVMs reperfused twice, though the reperfusion type was different from initial reperfusion type in only 2 of these (only these 2 included in totals). Five patients with reperfused PAVMs did not undergo repeat TCE; all were CP cases. These cases all had very small feeding arteries (<1 mm), and we suspected that blood flow came from normal capillary beds (oxygenated blood rather than shunted blood). Surgery was not performed for any reperfused PAVMs.

Clinical Follow-Up

During the follow-up period, there were no hemorrhagic complications from PAVMs. There was one neurologic complication (cerebral abscess) in a patient with diffuse PAVMs and previous cerebral abscess (diffuse patient 10). There were 6 deaths. Two deaths were unrelated to PAVMs or HHT: motor vehicle accident (focal patient 6) and massive gastrointestinal bleeding documented to be secondary to gastric ulcer (focal patient 1). Four deaths were related to HHT, and all occurred in patients with diffuse PAVMs. Diffuse patient 8 died 16 years after TCE as the result of circulatory arrest after lung transplantation at an outside hospital. Diffuse patient 7

Table I. Clinical characteristics of 42 children with PAVMs and classified by focal versus diffuse nature of PAVMs

Clinical manifestation	Focal group	Diffuse group	Total group
Exercise intolerance*	16/30 (53%)	8/12 (67%)	24/42 (57%)
Cyanosis	13/30 (43%)	12/12 (100%)[‡]	25/42 (60%)
Clubbing	10/30 (33%)	9/12 (75%)[‡]	19/42 (45%)
Hemoptysis	1/30 (3%)	2/12 (17%)	3/42 (7%)
TIA	0/30 (0%)	1/12 (8%)	1/42 (2%)
Stroke[†]	4/30 (13%)	2/12 (17%)	6/42 (14%)
Cerebral abscess	0/30 (0%)	2/12 (17%)[‡]	2/42 (5%)

*Either exercise intolerance or dyspnea on exertion.
[†]No patient had history of clinical stroke though a total of 6 patients had cerebral infarct on screening MRI (performed in 34 patients to screen for cerebral arteriovenous malformations).
[‡]P < .05 for comparison to the focal group.

died of complications of intrahepatic shunt for liver telangiectasias. Diffuse patient 10 died of a cerebral abscess, as above, after 16 years of follow-up. Diffuse patient 5 died of pneumonia complicated by pneumothorax.

Complications of TCE

Self-limited pleurisy occurred in 18 of 76 TCE sessions (24%). Deployment complications were rare, with no paradoxical embolization but two cases of coil misplacement (3% of TCE sessions and 1% of PAVMs). The remaining complications each occurred in one patient only (1% of TCE sessions, 0.5% of PAVMs): transient intraprocedure angina (focal patient 4), severe perioral pain, intraprocedure leg pain (diffuse patient 11), and transient brachial plexus injury caused by prolonged lateral decubitus position with arm extension (diffuse patient 6). There were no long-term complications.

DISCUSSION

PAVMs have been well described in adults, but there is a paucity of literature regarding the presentation and management of PAVMs in children. We report 42 children with PAVMs, the largest series in the literature to date, describing the safety and efficacy of TCE. We have demonstrated that children with PAVMs can have life-threatening complications. Yet, these patients can be treated safely and efficaciously with TCE.

PAVMs can lead to symptoms and complications in children. More than half of the children in our series presented with exercise intolerance, cyanosis, or clubbing. Neurologic complications were less frequent than in adults but had occurred in 19% of subjects before treatment. Neurologic and hemorrhagic complications occurred predominantly in cyanotic patients. We report a greater proportion of patients with diffuse PAVMs at 29%, compared with 5% in adults.[2,13] This probably reflects referral bias, in that patients with more severe disease are more likely to be diagnosed early. Although patients with diffuse PAVMs had a more severe clinical

presentation, neurologic and hemorrhagic complications also occurred in those with focal PAVMs.

The angioarchitecture and distribution of focal PAVMs in our series of children is similar to that reported in adult series.[2,3,14] Most PAVMs were simple (78%), were located in the lower lobes (73%), and were multiple (60%).

TCE efficacy in children is similar to that in adults. As in adults, we observed significant improvement in oxygenation after TCE. In adults, reperfusion occurs in 10% to 15% of PAVMs on long-term follow-up.[4,14] We demonstrated the reperfusion rate to be 15% in children, representing 45% of patients, despite the extensive experience of the interventional radiologists. This estimate of reperfusion rate may be an overestimate because we included patients with CP of PAVMs, though these collaterals may not in fact lead to shunting of blood to the venous sac but rather consist of collateral arteries with capillaries draining into the venous sac. We opted not to retreat several PAVMs reperfused by CP because feeding arteries were tiny (1 mm), and these children had no deterioration in oxygenation. Reperfused lesions were successfully retreated with TCE. The 15% reperfusion rate in children reinforces the need for long-term follow-up.

We have demonstrated that TCE of PAVMs in children is relatively safe, with complication rates similar to adult rates. In our series, pleurisy occurred after 24% of TCE sessions, compared with 10% to 30% in adults.[2,4,6] Deployment complications occurred in less than 3% of sessions, similar to the rate in adults.[2,4,6] We observed no long-term complications of TCE. Technical aspects of TCE were similar to those previously described for adults,[6] with the addition of general anesthesia or heavy sedation.

There are some limitations to the current study. First, this is a retrospective series with no control group. It is considered unethical to randomly assign adults with PAVMs to potentially receive no treatment because untreated PAVMs can cause life-threatening complications. For this reason, we believed that retrospective data would provide an ethical first attempt at assessing safety and efficacy of TCE in children. Second, though we included all children with PAVMs who were treated at the three centers, we did not include untreated children from these centers. We might speculate that this selection bias influenced efficacy and safety data if the PAVMs "easiest to treat" were included, but in fact this is unlikely because our series shows a much higher prevalence of patients with diffuse PAVMs (severe disease) than any adult series and therefore the bias would more likely have caused us to underestimate safety and efficacy. Third, we did not address the question of relative efficacy of various embolic devices, but there is no significant difference in adults.[15,16] Finally, all patients underwent TCE at highly specialized HHT centers, with experienced interventional radiologists, and therefore the results are probably not generalizable to other centers.

TCE should therefore be considered the treatment of choice for children, as in adults. With the favorable safety and efficacy of TCE in children and adults, there is no clear role for surgery in the management of PAVMs. This is particularly true in children, who may have development of more PAVMs or enlargement of small PAVMs later in life, requiring repeat therapy. In our series, repeat TCE carried no incremental risk, though multiple surgical resections could result in significant morbidity. Children with cyanosis, exercise intolerance, growth delay, or previous complications of PAVMs should be treated with TCE. With the 15% reperfusion rate of PAVMs after TCE in children, it might be reasonable in the acyanotic asymptomatic child (without previous complications) to delay treatment until after age 5 years, or even adolescence.

We have no data on the use of TCE in infants, as our youngest child treated was 4 years old.

It is currently recommended that adults with HHT be screened for PAVMs, based on the rationale that TCE can prevent serious complications from PAVMs. In children, there have been no screening studies reported to date, but the rationale for screening would be similar. Screening with contrast echocardiography has been shown to be a sensitive screening test in adults with HHT,[1] though there is little experience in children to date. Further studies are needed to determine a screening strategy for children, but this should include a minimum of chest radiography and oximetry, because most complications occur in cyanotic patients, and could include relatively noninvasive contrast echocardiography.

We conclude that PAVMs cause serious complications in children and that treatment with TCE is safe and efficacious. We recommend that children from HHT families be screened for PAVMs and treated with TCE, depending on age and risk of complications.

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50 Years Ago in *The Journal of Pediatrics*

USE OF A QUADRUPLE SULFONAMIDE MIXTURE IN ACUTE BACTERIAL INFECTIONS IN INFANCY AND CHILDHOOD

Ferguson AD, Kessler AD, Scott RB. J Pediatr 1954;45:656-61.

The authors make a strong defense for sulfonamide-therapy, which had a track record in children dating back to 1933, during a period when alternatives such as penicillin (1941), chloramphenicol (1947), tetracycline (1948), and streptomycin (1949) were rapidly emerging. The basis for their defense was the good oral tolerance, well-established security profile and low cost. Today, the argumentation for use of "old" antimicrobials, penicillin, for example, versus new, more sophisticated alternatives continues to be based on similar grounds: a good track record. The current need is for new alternatives to cover pathogens with complicated antimicrobial resistance patterns, a new scenario.

The authors focus their work on treatment of "bacterial" respiratory infections; however the experimental design is weak compared to today's standards. There are no clear definitions for bacterial infection, inclusion and exclusion criteria, nor for safety parameters to be evaluated, there is no method for determining sulfonamide plasmatic levels and a number of treatment schedules are used.

The report shows us the limitations at that time for conducting high-standard clinical research, some of which remain to date. There was minimal understanding of the microbiological origin of upper and lower respiratory infections in the 1950s. The difficulty in establishing an etiological diagnosis in lower respiratory infections continues to pose a significant challenge and more often than not, is unsuccessful. For tonsillitis, we have learned that only streptococcal infections are worth treating with antibiotics and that sulfonamides are not a good alternative for this indication.

Sulfonamide-therapy was widely used for respiratory, skin, and meningeal infections (for the latter combined with penicillin and chloramphenicol) because of its activity against *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Neisseria meningitides.* In addition, sulfonamide-therapy was recommended for prophylaxis of meningococcal infection and for urinary tract infections caused by enteric Gram-negative rods. Unfortunately, in a short time period, a significant proportion of these microorganisms became sulfonamide-resistant. In the 1970s, sulfonamide-therapy reemerged as a combination drug, trimethoprim-sulfamethoxazole, for enteric and respiratory infections, this excellent alternative has also suffered the fate of rapid spread of resistance caused by massive prescription practices. An erythromycin-sulfisoxazole combination developed for upper respiratory infections caused by *S pneumoniae* and *H influenzae* had a shorter life.

In the 2000s, sulfonamide-therapy continues to have a place in the treatment or prophylaxis of specific clinical conditions such as *Pneumocystis jiroveci* pneumonia, Toxoplasmosis, Isosporosis, Typhoid fever, Pertussis, Nocardiosis, and Listeriosis.

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