Treatment of infections caused by multi-resistant microorganisms in hospital at home units

Unidad de Hospitalización a Domicilio. Hospital Universitario de Torrejón. Grupo de Trabajo de Hospitalización a Domicilio y Telemedicina de la SEMI. Universidad Francisco de Vitoria.

Manuel Mirón-Rubio

ABSTRACT

Hospital at home units allow the treatment of moderate and severe infections by administering intravenous antibiotics to patients who would otherwise have to remain hospitalised. Increasing antibiotic resistance adds an element of difficulty to outpatient treatment of infections because multiple daily doses of antimicrobials or combinations of antimicrobials are sometimes required. This manuscript discusses some of the challenges of outpatient management of infections with multidrug-resistant microorganisms and shows the main antibiotic resistances and the outcomes of treatment of these infections in Spanish home hospitalisation units.

Keywords: multidrug-resistant microorganisms, hospital at home, OPAT, intravenous antibiotic treatment.

Infections caused by multi-resistant microorganisms represent a challenge for healthcare organisations, not only because of the risk to patients, but also because of the consumption of resources. In hospitals, multidrug-resistant infections force beds to become unusable to ensure isolation measures, and the frequent need to treat these infections with intravenous antibiotics results in prolonged hospital stays.

Outpatient treatment of these infections can help relieve hospital pressure and, in turn, reduce the risk of nosocomial infections. However, treating infections caused by multidrug-resistant microorganisms at home presents a new challenge. The lack of room temperature stability of some antimicrobials that are administered several times a day intravenously or the need to combine antibiotics to broaden the spectrum or achieve synergies can make home therapy difficult.

For this reason, the choice of antibiotic for outpatient treatment is sometimes made on the basis of ease of administration regardless of clinical practice guidelines and recommendations. In one study, outpatient therapy with antibiotics administered as a single daily dose was found to be inadequate in 28% of patients [1]. Therefore, the choice of antimicrobial should not be based on the ease of administration of the drug, as this may lead to further resistance or therapeutic failure; this decision should rather be based on its activity, efficacy and safety profile.

The appropriateness of the use of parenteral antibiotics in the outpatient setting is related to the organisation, resources and competence of the team treating and monitoring patients with infectious conditions. These circumstances may also influence treatment outcomes. Salles et al. observed that a lack of medical visits was a predictor of readmission and mortality for patients receiving outpatient antimicrobial therapy [2].

The home hospitalisation model is staffed by healthcare professionals with hospital dependency and training who monitor and control patients on a daily basis. This model allows early identification of complications and control of the evolution of the infectious process, and may explain why the therapeutic success rate is over 90% and the return rate to hospital is less than 8% in large series of cases [3]. Even so, the risk of treatment inadequacy remains [4].

Regardless of the care model, outpatient parenteral antimicrobial therapy cannot be considered as an isolated procedure, but as an organised process that includes criteria for the selection of patient, drug, venous access route and infusion modality, daily monitoring of infection evolution, indication and interpretation of complementary tests, de-escalation and sequencing of antibiotics when indicated, duration of treatment, discharge planning and subsequent follow-up [5]. The need to ensure safe and effective outcomes has recently prompted the development of quality indicators for the practice of outpatient parenteral antimicrobial therapy [6].

In addition, in the case of multidrug-resistant microor-
organisms, the choice of antimicrobials should take into account risk factors for resistance. Carrier states, high local incidence, recent hospitalisation, recent and repeated use of antibiotics, instrumental manipulations and health care are all risk factors for antibiotic resistance. For each microorganism there are, in addition, some specific risk factors [7,8].

One aspect not yet fully resolved is the stability of some antimicrobials at room temperature. This property of drugs is crucial as lack of stability limits the home use of antibiotics that are administered more than once a day. When nursing shifts allow, antimicrobials can be administered every 12 hours, even if they are not stable. For the rest, the solution is refrigeration in a refrigerator and self-administration, or infusion via systems that allow the dilution to be kept refrigerated. The latter is not sufficiently widespread and has the disadvantage of the need to incorporate a temperature control system and direct infusion of a cold dilution into the vein, which can be uncomfortable for the patient.

Meropenem is an example of an antibiotic for which there is a discrepancy between laboratory stability and clinical use. While most sources do not give this drug a room temperature stability of more than 12 hours at different concentrations and with different diluents, some authors have successfully used it in continuous infusion without refrigeration [9,10].

For drugs that are not stable at room temperature for 24 hours, self-administration of antibiotics intravenously is a safe procedure. It requires that the patient or caregiver is trained, properly instructed and supervised by health care personnel [11,12]. Today, self-administration is used even for stable drugs or antibiotics administered as a single daily dose.

Another aspect that has not been sufficiently analysed in outpatient antimicrobial therapy is the application of PK/PD principles [13]. In the presence of microorganisms with high MIC, the same recommendations should be followed as for any other patient, as well as for cases where the spectrum of activity or synergistic effect needs to be broadened by combining drugs. However, the benefit of strategies such as extended or continuous infusion of antibiotics in patients in the defervescent stage of infection, as in many of the patients seen in hospital at home, is less clear. Therefore, these strategies, and their efficacy compared to intermittent infusion in the outpatient setting, require further study to recommend their use [14].

Despite the rise of multidrug-resistant infections and the increasing activity of outpatient parenteral therapy, there are still few studies that specifically analyse the results of this practice in this type of infections. However, the available data suggest that the efficacy of treatment, both in targeted and empirical therapy, is comparable to those caused by sensitive microorganisms.

The registry of intravenous home antimicrobial therapy (TADE Registry) records infection treatment activity in Spanish home hospitalisation units. From July 2011 to December 2020, more than 12,000 episodes of infections treated at home were included. The registry analyses the microorganisms causing the infection and the pattern of antibiotic sensitivity of some of them to the main groups of antibiotics. Table 1 shows the main Gram-positive and Gram-negative microorganisms causing infections and the proportion of resistance to various antibiotics. Table 2 shows the percentage of cure or improvement of infections for each of them and the 30-day hospital readmission rate.

### Table 1

| Microorganism          | Total isolates | Isolates with antibiotic resistance, n (%) |
|------------------------|----------------|--------------------------------------------|
|                        |                | Amoxicillin-clavulanate | Ampicillin | Ceftriaxone | Ciprofloxacin | Ertapenem | Gentamicin |
| Escherichia coli       | 2,657          | 932 (35.1)            | 1710 (64.4) | 856 (32.2) | 1325 (49.9) | 18 (0.7)  | 479 (18.0) |
| Proteus mirabilis      | 229            | 67 (29.3)             | 122 (53.3)  | 47 (20.5)  | 116 (50.7)  | 11 (4.8)  | 60 (26.2)  |
| Klebsiella pneumoniae  | 685            | 327 (47.7)            | 518 (75.6)  | 347 (50.7) | 373 (54.5)  | 29 (4.2)  | 190 (27.7) |
| Enterobacter cloacae   | 168            | 135 (80.4)            | 124 (73.8)  | 72 (42.9)  | 55 (32.7)   | 6 (3.6)   | 27 (16.1)  |
|                        |                | Amikacin               | Ceftazidime | Ciprofloxacin | Gentamicin | Imipenem-clavulanate | Piperacillin-tazobactam |
| Pseudomonas aeruginosa | 1650           | 144 (8.7)             | 307 (18.6)  | 951 (57.6) | 518 (31.5)  | 426 (25.8) | 342 (20.7) |
|                        |                | Ciprofloxacin          | Cloxacillin | Trimethoprim-sulfamethoxazole | Daptomycin | Penicillin | Vancomycin |
| Staphylococcus aureus  | 559            | 138 (24.7)            | 171 (30.6)  | 30 (5.4)   | 8 (1.4)     | 361 (64.6) | 18 (3.2)   |
| Staphylococcus epidermidis | 177    | 92 (52.0)             | 103 (58.2)  | 71 (40.1)  | 3 (1.7)     | 108 (61.0) | 6 (3.4)    |
|                        |                | Ampicillin             | Daptomycin  | Gentamicin  | Linezolid   | Penicillin | Vancomycin |
| Enterococcus faecalis  | 328            | 15 (4.6)              | 6 (1.8)     | 83 (25.3)  | 3 (0.9)     | 20 (6.1)  | 3 (0.9)    |
These data suggest that treatment of infections caused by multidrug-resistant microorganisms in hospital at home is common and effective, although with differences depending on the microorganism and the antibiotic(s) to which it is resistant. The organisation of these units with doctors and nurses following up patients on a daily basis may explain these good results. However, more information is needed on the appropriateness of antimicrobial treatment to clinical practice guidelines and recommendations in the home setting.

ACKNOWLEDGEMENTS

Spanish Hospital at Home Intravenous Antimicrobial Therapy Registry (TADE Registry) researchers

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

REFERENCES

1. Britt RS, LaSalvia MT, Padival S, Patel P, McCoy C, Mahoney MV. Evaluation of inpatient antimicrobial regimens for readmitted outpatient parenteral antimicrobial therapy patients receiving daptomyc in or ertapenem for ease of administration. Open Forum Infect Dis. 2019;6(12):ofz496. doi: 10.1093/ofid/ofz496. PMID: 3212833.

2. Salles TCG, Cerrato SG, Santana TF, Medeiros EA. Factors associated with successful completion of outpatient parenteral antibiotic therapy in an area with a high prevalence of multidrug-resistant bacteria: 30-day hospital admission and mortality rates. PLoS One. 2020;15(11):e0241595. doi: 10.1371/journal.pone.0241595.

3. Mirón-Rubio M, González-Ramallo V, Estrada-Cuxart O, Sanroma-Mendizabal P, Segado-Soriano A, Mujal-Martínez A, et al. Intravenous antimicrobial therapy in the hospital-at-home setting: data from the Spanish Outpatient Parenteral Antimicrobial Therapy Registry. Future Microbiol. 2016;11(3):375-390. doi: 10.2217/fmb.15.141.
4. Sánchez Fabra D, Ger Buil A, Torres Courchoud I, Martínez Murgui R, Matia Sanz MT, Fiteni Mera I, et al. Antimicrobial management in community acquired pneumonia in hospital at home: Is there room for improvement? Enferm Infect Microbiol Clin. 2020;50:213-005X(20)30311-6. doi: 10.1016/j.eimc.2020.10.002.

5. López Cortés LE, Muñoz Martínez A, Fernández Martínez de Mandojana M, Martín N, Gil Bermejo M, Solà Aznar J, et al. Executive summary of outpatient parenteral antimicrobial therapy: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases and the Spanish Domiciliary Hospitalisation Society. Enferm Infect Microbiol Clin. 2019;37(6):405-409. doi: 10.1016/j.eimc.2018.03.012. Epub 2018 May 18. PMID: 29784453.

6. Berrevoets MAH Ten Oever J, Oerlemans AJM, Kullberg BJ, Hulscher ME, Schouten JA. Quality indicators for appropriate outpatient parenteral antimicrobial therapy in adults: a systematic review and RAND-modified Delphi procedure. Clin Infect Dis. 2020;70(6):1075-1082. doi: 10.1093/cid/ciz362.

7. Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Ruiz M, Peña C, et al. Community-onset bacteraemia due to extended-spectrum B-lactamase-producing Escherichia coli: risk factors and prognosis. Clin Infect Dis. 2010;50:40-8. doi: 10.1086/649537.

8. Defez C, Fabbro-Peray P, Bouziges N, Gouby A, Mahamat A, Daurès J-P, et al. Risk factors for multidrug-resistant Pseudomonas aeruginosa nosocomial infection. J Hosp Infect. 2004;57(3):209-16. doi: 10.1016/j.jhin.2004.03.022.

9. Perks SJ Lanskey C, Robinson N, Pain T, Franklin R. Systematic review of stability data pertaining to selected antibiotics used for extended infusions in outpatient parenteral antimicrobial therapy (OPAT) at standard room temperature and in warmer climates. Eur J Hosp Pharm Sci Pract 2019;0:1-8. doi: 10.1136/ehjp-2019-001875.

10. Legg A, Halford M, McCarthy K. Plasma concentrations resulting from continuous infusion of meropenem in a community-based outpatient program: A case series. Am J Health Syst Pharm. 2020;77(24):2074-208. doi: 10.1093/ajhp/zxaa319.

11. Pajaron M, Fernández-Miera MF, Allende I, Amria AM, Gutiérrez-Cuadra M, Cobba-Belaustegui M, et al. Self-administered outpatient parenteral antimicrobial therapy (S-OPAT) for infective endocarditis: a safe and effective model. Eur J Intern Med. 2015;26(2):131-6. doi: 10.1016/j.ejim.2015.01.001.

12. Matthews PC, Conlon CP, Berendt AR, Kayley J, Jeffries L, Atkins BL, et al. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother. 2007;60(2):356-62. doi: 10.1093/jac/dkm210.

13. Slavik RS, Jewesson PJ. Selecting antibacterials for outpatient parenteral antimicrobial therapy pharmacokinetic-pharmacodynamic considerations. Clin Pharmacokinet, 2003;42(9):793-817. doi: 10.2165/00003088-200342090-00002.

14. García-Queiruga M, Feal Cortizas B, Lamelo Alfonsin F, Pertega Diaz S, Martín-Herranz I. Continuous infusion of antibiotics using elastomeric pumps in the hospital at home setting. Rev Esp Quimioter. 2021;garcia16mar2021. doi: 10.37201/req/122.2020.