Azotemia induced by tigecycline☆

Azoemia inducida por tigeciclina

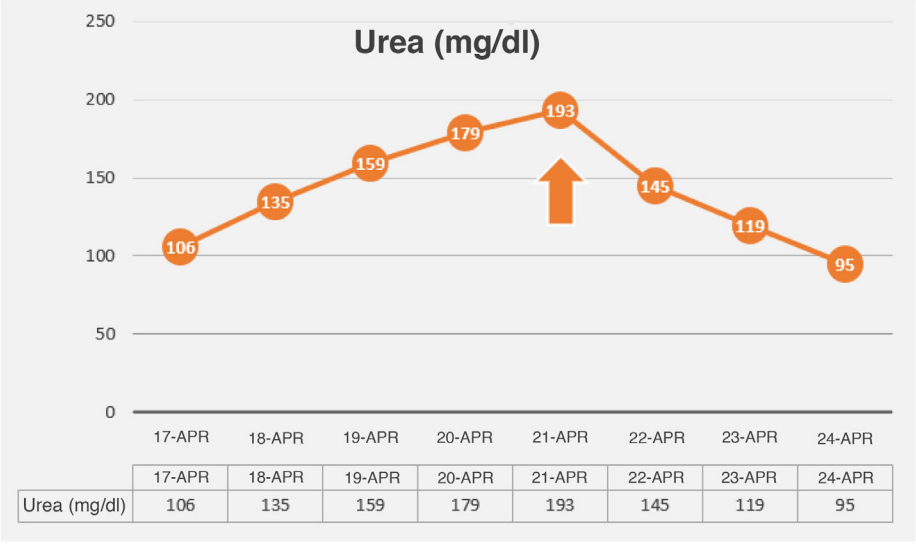
In response to the need for new antibiotics, the late 1940s witnessed the development of the first tetracyclines obtained from different species of *Streptomyces* spp.

As the intensive use of tetracyclines in both humans and the veterinary industry led to the emergence of bacterial resistance, new semi-synthetic tetracyclines were developed, particularly tigecycline[1]. The relatively limited antimicrobial spectrum of the classic tetracyclines, the fact that they cannot be used in children or during pregnancy or lactation, and the emergence of new, more effective components in other families of antibiotics, all prompted a gradual decline in the use of tetracyclines in humans[2]. Nevertheless, certain tetracyclines are still used in routine clinical practice, mainly due to their broad spectrum of action, with activity against multiresistant microorganisms, in addition to being a therapeutic alternative for patients with allergies to other antibiotics.

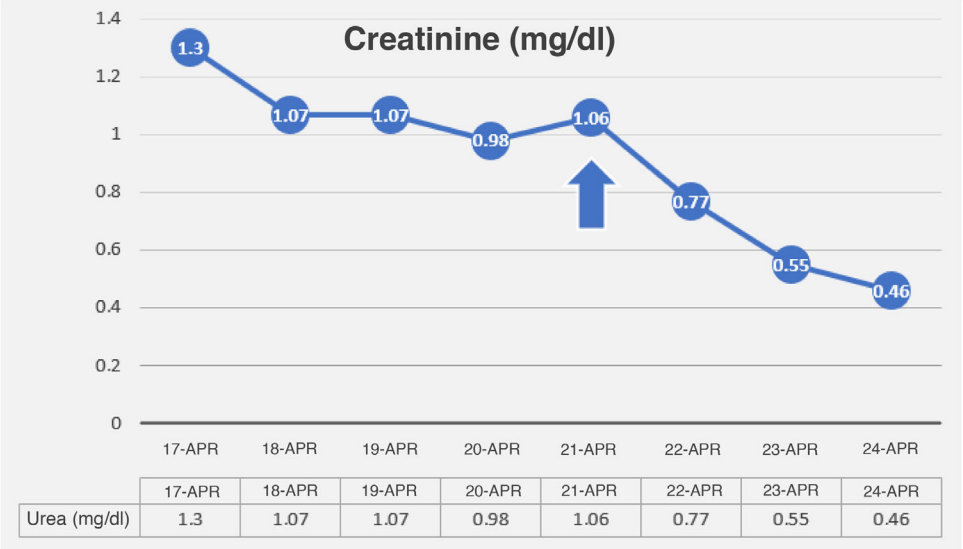
We present the case of a 73-year-old female patient, allergic to penicillins, with a medical history of hypertension, dyslipidaemia and hypothyroidism.

The patient came to the Accident and Emergency Department with poor general condition and a one-month history of a painful neck tumour. In the initial assessment, she was conscious and orientated, with adequate distal perfusion and mild tachypnoea. Her baseline oxygen saturation was 95%, mean arterial pressure 50 mmHg, with sinus tachycardia of 100 bpm and a temperature of 37.8 °C. Blood results showed acute kidney failure, with creatinine 2 mg/dl, urea 134 mg/dl, glomerular filtration rate 24 ml/min/1.73 m^2, procalcitonin 2 ng/ml and leucocytes 9,300/mm^3.

The computed tomography of the neck revealed extensive bilateral inflammatory involvement on the anterior neck, with



	17-APR	18-APR	19-APR	20-APR	21-APR	22-APR	23-APR	24-APR
Urea (mg/dl)	106	135	159	179	193	145	119	95



	17-APR	18-APR	19-APR	20-APR	21-APR	22-APR	23-APR	24-APR
Urea (mg/dl)	1.3	1.07	1.07	0.98	1.06	0.77	0.55	0.46

Fig. 1. Changes in analytical data. The arrow indicates the day tigecycline was discontinued.

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Table 1
Application of the modified Karch and Lasagna algorithm.

Assessment criterion	Classification	Description	Score
Time sequence	Consistent	The adverse event described (hyperazotaemia) appears during or after the administration of the medicinal product (tigecycline) and is consistent with the drug's mechanism of action or with the idiosyncratic process	+2
Previous knowledge	Well-known ADR	Causal relationship listed in the summary of product characteristics	+2
Effect of withdrawal of suspected medicinal product	Improvement of ADR	The event improves on withdrawal of the medicinal product, regardless of the treatment received	+2
Effect of re-exposure to the suspected medicinal product	There is no re-exposure	There was no re-exposure	0
Existence of alternative causes	There is information that rules out an alternative explanation	There is enough information not to suspect an alternative cause. There is no plausible association between the underlying disease or other medication taken simultaneously with the causal relationship studied	+1
Contributing factors that support the assessment of causality	None or unknown	Factors in the suspected medicinal product which may have contributed to the occurrence of the adverse reaction	0
Complementary explorations	There are complementary explorations	Serial analytical data obtained	+1

multiloculated abscess-like fluid collections. Urgent surgery was performed, with drainage of the purulent collections of fluid and debridement of adjacent structures. The patient was transferred to the Intensive Care Unit, sedated with analgesia and connected to mechanical ventilation. She was given empirical antibiotic therapy at an initial dose of 100 mg, followed by 50 mg every 12 h and clindamycin (600 mg every 8 h). *Streptococcus anginosus* was isolated from an intraoperative sample of the neck abscess.

Over the following days, the patient's infectious condition was seen to improve. However, blood tests showed a persistent metabolic acidosis despite adequate haemodynamic resuscitation, with the need for low-dose noradrenaline for a mean arterial pressure of 65 mmHg. She presented dissociation of the urea/creatinine ratio, with elevation of urea levels to a maximum peak of 193 mg/dl, with creatinine 1.06 mg/dl and hyperphosphataemia. Adequate diuresis was maintained without the need for diuretics; her liver profile was within the normal range. However, severe myopathy delayed the withdrawal of the mechanical ventilation despite adequate oxygenation.

Following an exhaustive study of the case and a literature review, this analytical and clinical finding was interpreted as an adverse effect of tigecycline. After 96 h, the tetracycline was withdrawn from the treatment and replaced with levofloxacin. 24 h after the withdrawal, the patient's urea levels had fallen to 145 mg/dl, with creatinine 0.77 mg/dl and improvement of the metabolic acidosis. The evolution in the analytical data are shown in Fig. 1.

The Karch and Lasagna algorithm was applied to confirm the causal relationship of the adverse effect with tigecycline and a total score of 8 points was obtained, demonstrating a definite relationship between both events[3] (Table 1).

We should also point out that according to the literature, none of the other treatments given to the patient as of her admission to the intensive care unit (remifentanil, propofol, dexmedetomidine, total parenteral nutrition, noradrenaline, vitamin K, omeprazole, paracetamol and clindamycin) has any obvious relationship with the increase in plasma urea.

Hyerazotaemia can have an extrarenal cause, due to increased production of urea secondary to high-protein diets, gastrointestinal bleeding, situations that increase protein catabolism (sepsis, multiple trauma, stress, etc) or drugs that inhibit anabolic metabolism (tetracyclines and corticosteroids). A renal cause for the increase in plasma urea is also possible, considering three different types: (a) prerenal due to absolute hypovolaemia (gastrointestinal, renal and skin losses and third space sequestration) or relative hypovolaemia (hepatorenal syndrome, heart failure, liver cirrhosis, nephrotic syndrome, consumption of NSAID or ACE inhibitors); (b) of parenchymal origin, due to acute tubular necrosis, glomerulopathy, tubulointerstitial nephropathy (aminoglycosides, vancomycin, amphotericin B, cephalosporins, anaesthetics, ciclosporin, tacrolimus, radiological contrast agents, pigments [myoglobin, haemoglobin], metals and systemic diseases [sarcoidosis, tuberculosis, Sjögren's syndrome, multiple myeloma]); and (c) of post-renal aetiology, due to decreased glomerular filtration resulting from obstruction to urine flow in any part of the urinary tract, intrinsic obstruction (clots, crystals, casts) or extrinsic obstruction (prostatic disease, retroperitoneal fibrosis or neoplasms)[4].

Reviewing the published literature, we found several authors who, as far back as the 20th century[5–10], detected a clinical picture of metabolic acidosis, hyperazotaemia and hyperphosphataemia in patients on treatment with tetracyclines. The withdrawal of the antibiotic from the treatment reversed the laboratory abnormalities in most cases, regardless of the patient's renal function prior to the acute disease. These authors associated this adverse event with the antianabolic effect of tetracyclines.

According to the summary of product characteristics issued by the Spanish Agency of Medicines and Medical Devices, unlike other tetracyclines, tigecycline does not require dose adjustment to renal function. We believe that the publication of this case is important due to the high degree of clinical suspicion required for diagnosis, as well as the need to investigate the underlying pathophysiological mechanism and to reassess whether this antibiotic requires stricter control in patients with impaired renal function. These factors are particularly important since, while stigmatised in the past, tetracyclines continue to be a valuable treatment option in our day-to-day practice.

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Changes in the incidence and clinical manifestations of paediatric respiratory infections of viral aetiology during the SARS-CoV-2 pandemic☆

Cambios en la incidencia y manifestaciones clínicas de las infecciones respiratorias pediátricas de etiología vírica durante la pandemia por SARS-CoV-2

Following the declaration of the state of alarm due to the SARS-CoV-2 pandemic on 14 March 2020 in Spain, the number of respiratory infections in paediatrics fell considerably. The transmission of viral infections occurs mostly through respiratory droplets, aerosols or fomites. Home confinement, the closure of schools and the mandatory wearing of face-covering have led to a change in the epidemiology of common viral infections, with a significant decrease in viral epidemics such as influenza or acute bronchiolitis.[1,2]

The objective of this study was to analyse the incidence and changes in the aetiology of infections caused by respiratory viruses in paediatrics during the SARS-CoV-2 pandemic. We carried out a single-centre retrospective observational study in the Paediatric Department of a tertiary hospital. We compared respiratory viral infections from two year-long periods: 14 March 2020 to 14 March 2021 (CoV-period) versus the same time interval for the previous year, 2019-2020 (pre-CoV period). Our centre uses a commercial real-time technique that simultaneously and differentially detects 21 respiratory viruses (Allplex Respiratory Assay-Seegene, South Korea). The PCR test for SARS-CoV-2 is performed using a commercial real-time RT-PCR technique (Allplex 2019-nCov Assay-Seegene and the TaqPathTM COVID-19 CE-IVD RT-PCR-Kit). The data were obtained from the electronic registry of the hospital's medical records.

During the year of the pandemic (CoV-period), there was a 68% reduction in visits to the Accident and Emergency for respiratory disease (CoV-period 2,455, pre-CoV 7,697) and a 63% reduction in respiratory admissions (CoV-period 263, pre-CoV 713). During the pandemic, a total of 1,144 PCR were analysed, representing a decrease of 51% compared to the pre-CoV period, with an overall positivity percentage of 6% vs 10% pre-Cov period (CoV-period 416, pre-CoV 1,365; $p < 0.01$).

The median age of patients with viral respiratory infection was 26 months; interquartile range (IQR) 64-147 (pre-CoV 25 months, IQR 55-136, $p = 0.04$). There was an increase in patients seen in the 6-9 year-old age group, representing 12.3% (pre-CoV 10.8%; $p < 0.01$), and in over-10 year-olds, which was 9.5% (pre-CoV 7.4%, $p < 0.01$).

Fig. 1 shows the incidence of the main respiratory viruses and changes over the study period. All the viruses showed a decrease in the positivity rate of the samples analysed. The viruses which decreased the least during the pandemic were: rhinovirus, with 238 cases during the COV-period (pre-CoV 440; $p < 0.01$); adenovirus, with 48 cases during the CoV-period (pre-CoV 161; $p < 0.01$); and enteroviruses, with 33 cases in the CoV-period (pre-CoV 125; $p < 0.01$). A total of 98 SARS-CoV-2 infections were detected in our hospital.

Regarding the respiratory infectious aetiology, the most significant decrease was found in acute bronchiolitis, being 91.4%

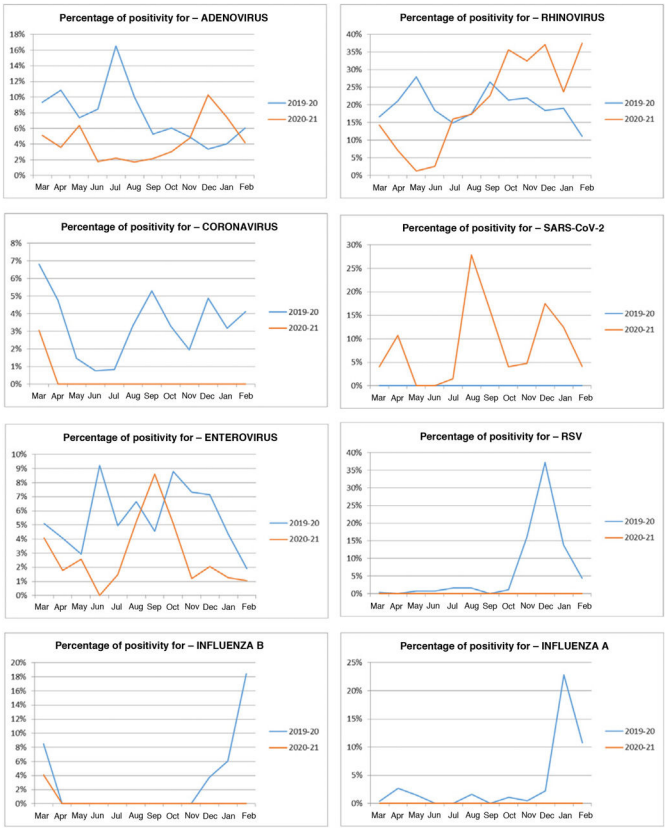

Figure 1. Incidence of the different respiratory viruses detected by PCR. 2019-2020 (pre-CoV period) – 2020-2021 (CoV-period).

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