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Ciência Aberta: Resposta de Emergência ou o Novo Normal?

Open Science: Emergency Response or the New Normal?

Eloy RODRIGUES✉[1]

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Palavras-chave: Acesso à Informação; COVID-19; Disseminação da Informação; Publicação
Keywords: Access to Information; COVID-19; Information Dissemination; Publishing

A pandemia de COVID-19 teve um impacto significativo na investigação e na publicação científica em todas as disciplinas (incluindo as Ciências Humanas e Sociais), mas refletiu-se de forma mais expressiva na área Biomédica. Para além de outros efeitos, a pandemia provocou a concentração da investigação no vírus SARS-CoV-2 e na doença COVID-19, e a adoção de práticas de investigação, partilha de resultados e publicação alinhadas com a ciência aberta.

Existem inúmeras definições de ciência aberta, mas, em síntese, este conceito refere-se à abertura dos processos e dos resultados (dados, publicações, código, etc.) de investigação, englobando várias componentes e práticas, facilitando a colaboração e aumentando a transparência e a reprodutibilidade.

A concentração da investigação em aspetos relacionados com a pandemia, em detrimento das outras áreas e temas de investigação, atingiu proporções inéditas e gerou resultados sem precedentes. De acordo com dados do sistema *Dimensions,* de janeiro a 1 de junho de 2020 foram produzidos 42 703 artigos de revistas, 3105 ensaios clínicos, 422 *datasets*, 272 patentes e 757 documentos de política.[1] No levantamento que realizámos no mesmo sistema no final de setembro de 2022, relativo ao biénio de 2021 - 2022, registavam-se 885 004 publicações, 15 715 ensaios clínicos, 29 431 *datasets*, 31 703 patentes e 33 057 documentos de política.[1]

Os resultados obtidos, em termos quantitativos, qualitativos e temporais (no conhecimento do vírus, da doença, na investigação de possíveis terapias, e no desenvolvimento de vacinas), não podem ser dissociados da adoção de práticas de ciência aberta na investigação e publicação. Desde logo na rápida partilha de conteúdos dedicados ao genoma do SARS-CoV-2, identificado nos casos iniciais da China, bem como dos primeiros casos que foram ocorrendo nos diferentes países à medida que o vírus se propagava por todos os continentes.

A partilha e abertura de dados e publicações foi uma das primeiras recomendações da Organização Mundial da Saúde e de várias outras organizações científicas e médicas por todo o mundo. E, de facto, relativamente aos dados, desde os primeiros meses de 2020 foram disponibilizadas dezenas de bases de dados, infraestruturas e ferramentas para o depósito, agregação, partilha e análise de informação, reaproveitando sistemas e serviços já existentes, ou através da criação de novas plataformas. A recolha e partilha de um grande volume e diversidade de dados sobre o SARS-CoV-2 e a COVID-19 contribuiu para a rápida geração de conhecimento científico e para a tomada de decisões políticas, apesar de existirem limitações na acessibilidade e problemas de qualidade de alguns dados, como os que se terão verificado em Portugal.[2]

Também na acessibilidade à literatura se verificaram mudanças significativas. Por um lado, a maioria dos artigos científicos relacionados com o vírus e a doença anteriormente publicados foram disponibilizados em acesso aberto em 2020. Além disso, registaram-se outras alterações, porventura mais relevantes, como a redução do tempo entre a submissão e a publicação dos artigos,[3] e o aumento da publicação de *preprints,* que na área Biomédica era ainda reduzida até ao início de 2020 (apesar do sucesso do repositório *bioRxiv*, nas Ciências Biológicas). O repositório para as Ciências da Saúde *medRxiv*, que recebia apenas entre 100 e 200 *preprints* por mês antes da pandemia, recebeu mais de 2000 *preprints* em maio de 2020.

O aumento deste tipo de publicações foi acompanhado pelo crescimento e consolidação de outras práticas e modelos inovadores, como a revisão por pares aberta e a publicação *overlay,* isto é, a publicação de conteúdos originalmente criados ou disponíveis em plataformas (como repositórios ou servidores de *preprints*) diferentes daquela em que o processo editorial e de publicação – controlo de qualidade, formatação, etc. – é realizado.

O comportamento adotado durante a pandemia proporcionou uma prova real das vantagens, e da exequibilidade, da ciência aberta. Tal como já tinha ocorrido anteriormente, por exemplo ao longo do surto de vírus Zika em 2015, a ciência aberta foi a resposta para a emergência. Mas será que a experiência da pandemia mudou para sempre o modo de realizar investigação e, passada a emergência, a ciência aberta se transformará no 'novo normal'? Ou, pelo contrário, nos próximos tempos regressaremos ao modelo

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tradicional abandonado durante a pandemia?

A consolidação e generalização das práticas de ciência aberta representa uma profunda mudança de paradigma na investigação e na comunicação científica. No que respeita à publicação científica, a mudança de paradigma passará pela propagação e generalização de práticas que têm vindo a ser adotadas nos últimos anos, e que ganharam maior visibilidade durante a pandemia. Desde logo, a mudança do modelo de "rever e só depois publicar", ainda predominante, para o modelo "publicar e depois rever". Associado ao crescimento da publicação de *preprints*, este modelo tem vindo a ser usado por atores importantes, como a revista *eLife*, que o adotou a partir de julho de 2021,[4] ou a plataforma de publicação da Comissão Europeia, *Open Research Europe*.[5]

A mudança para o modelo "publicar e depois rever", está também relacionada com outra alteração significativa. A passagem da revisão por pares 'cega' ou 'duplamente cega' para formas de revisão por pares aberta.[6] A revisão por pares aberta tem crescido lentamente, mas nos últimos anos proliferaram vários serviços e plataformas para revisões, comentários, validação e recomendação abertas. São exemplos, entre muitos outros, o *Peer Community in,*[7] ao qual diversas revistas confiam o seu processo de revisão por pares ou o *PREreview.*[8]

Finalmente, as duas mudanças acima referidas facilitam outra transformação, no sentido da publicação *overlay*, na qual as quatro funções principais da comunicação científica (registo, certificação, divulgação e arquivo) deixam de ser executadas pela mesma entidade, a revista científica, como tinha de acontecer no mundo da publicação em papel. Na era digital elas podem, com vantagem, ser distribuídas entre entidades diferentes, algumas das quais podem continuar a ser revistas, para as funções de certificação ou divulgação (Fig. 1).

A publicação *overlay* tem crescido nos últimos anos, ainda que a um ritmo igualmente lento.[9]

Por representarem uma mudança face a hábitos e condutas enraizadas, para que estas transformações possam alargar-se e consolidar-se como práticas correntes da generalidade da comunidade científica, será necessário reunir, pelo menos, três condições.

A primeira é que sejam conhecidas e compreendidas as vantagens da ciência aberta e dos modelos inovadores de publicação e disseminação dos resultados, para que os investigadores, as organizações de investigação e os financiadores de ciência, invistam o tempo e os recursos necessários para a transição. Apesar do exemplo recente da pandemia, não parece que isso já aconteça de um modo generalizado.

A segunda é a existência de serviços e infraestruturas abertos, modernos, sustentáveis, fáceis de usar e geridos pelas instituições ou comunidades. Esse ecossistema de infraestruturas institucionais/comunitárias já existe parcialmente, tendo um custo que é uma pequena fração do que se gasta atualmente com o sistema de publicação comercial. Mas necessita de ser completado, melhorado e de ser mais interoperável, de modo a facilitar a partilha e reutilização de informação entre sistemas, e a experiência dos utilizadores. Para isso é necessário que as instituições e consórcios, que presentemente suportam os custos das assinaturas de conteúdos comerciais, comecem a reorientar os seus fundos para infraestruturas e serviços abertos.

Em terceiro lugar, o requisito mais importante e mais difícil: a necessidade de alinhar o sistema de incentivos e recompensas com a promoção da ciência aberta. Nas últimas décadas, o modelo dominante na avaliação da investigação, dos investigadores e das suas instituições é

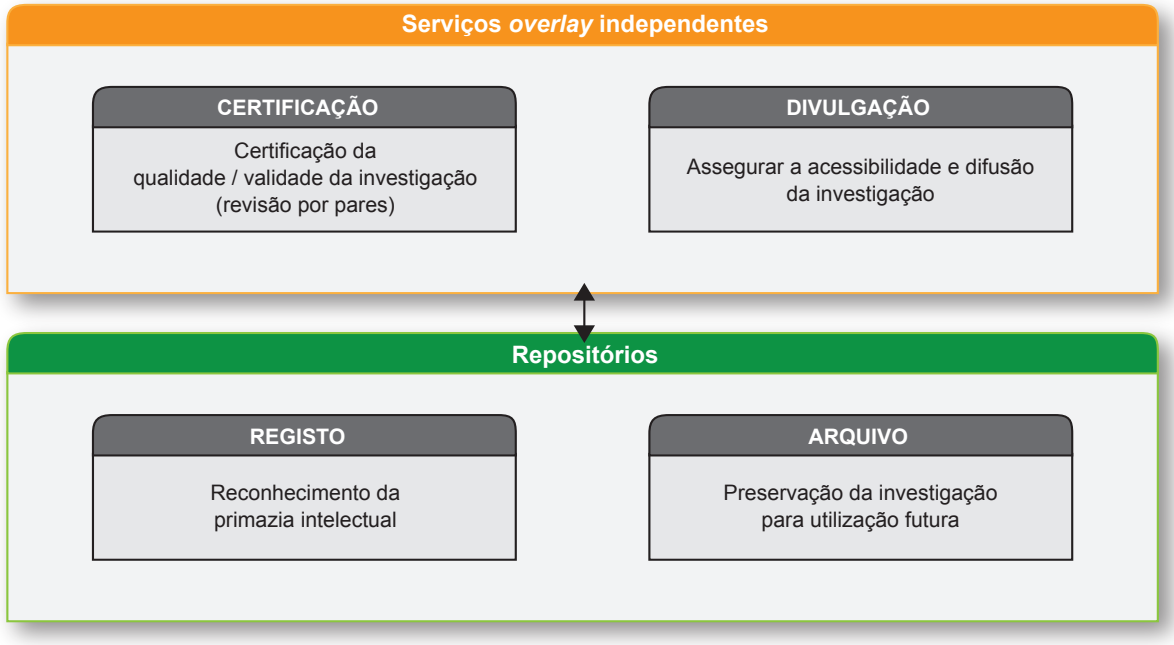

Figura 1 – Separação das funções da publicação científica

baseado em métricas de publicação e citação, e sobretudo métricas indiretas como o fator de impacto das revistas (que avaliam o contentor e não o conteúdo), e tem vindo a promover a cultura de "publicar o mais possível em revistas de maior impacto possível". Para além de outros problemas e impactos negativos (que afetam a qualidade, integridade e reprodutibilidade da ciência), este modelo de avaliação representa um forte obstáculo à mudança de comportamentos, e à adoção de novas práticas.

Para se alinhar com a ciência aberta, a avaliação da investigação e dos investigadores tem de ser mais ampla, valorizando todos os contributos e resultados (e não apenas as publicações), e de adotar uma perspetiva essencialmente qualitativa, baseada na revisão por pares, com utilização limitada e responsável de indicadores quantitativos. Também neste domínio se têm verificado progressos lentos, mas espera-se que os recentemente apresentados *Agreement on Reforming Research Assessment* e a *Coalition for Advancing Research Assessment*[10] possam acelerar e dar maior amplitude à transformação do processo de avaliação.

Se as três condições anteriormente enunciadas forem verificadas nos próximos anos, a ciência aberta deixará de ser apenas a ciência das emergências. E as práticas de investigação abertas e colaborativas, com rápida disseminação dos resultados, poderão passar a ser dominantes, sendo consideradas a forma correta de fazer ciência, sem necessidade de as designar de ciência aberta.

CONFLITOS DE INTERESSE

O autor declara a inexistência de conflitos de interesse.

FONTES DE FINANCIAMENTO

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Uso e Interpretação do Desenho Infantil na Prática Clínica

Use and Interpretation of Children's Drawing in Clinical Practice

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À semelhança da linguagem verbal e do jogo, o desenho é uma das manifestações semióticas da criança, enquanto meio de significação da realidade. Corresponde à primeira representação gráfica da criança, sendo um canal de comunicação entre esta e o mundo exterior, através do qual integra a imaginação e a realidade.[1-3]

Para além da expressão do seu estado emocional, a criança traduz no desenho o modo como se vê e como encara o seu papel no seio social e familiar, bem como as relações que estabelece. Por expressar o mundo interno da criança, o desenho é considerado um local de projeção privilegiado.[1-3]

O desenvolvimento do desenho vai evoluindo a par do desenvolvimento cognitivo e psicoafectivo, à medida que a criança cresce ao longo de cinco fases, segundo Piaget: Garatuja, Pré-esquematismo, Esquematismo, Realismo e Pseudo-naturalismo (ver Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18388/Apendice_01.pdf).[3]

O desenho infantil começa a ganhar destaque como instrumento de avaliação de capacidades cognitivas e de caraterísticas da personalidade no século passado. Em 1926, Goodenough defende o uso do desenho da figura humana para avaliar o nível de maturidade intelectual da criança. Os testes projetivos baseados em teorias psicodinâmicas evoluíram com trabalhos de Machover, desde 1949, e de Koppitz, desde 1968, que permitiam a avaliação de traços de personalidade e perturbações emocionais a partir de desenhos de figuras humanas. O desenho da família começa a ser utilizado por Minkowska em 1949 como modo privilegiado de expressão dos conflitos familiares. Para além da sua importância no diagnóstico, os desenhos começaram a ser utilizados como ferramenta terapêutica de inspiração psicanalítica com Melanie Klein.[3]

Hoje em dia, o desenho apresenta-se como um instrumento útil para todos os profissionais de saúde que trabalham com crianças, quer em contexto de ambulatório como de internamento, promovendo a criação da relação terapêutica e de diferentes formas de avaliação e de intervenção.[1-5] É um instrumento auxiliar para a aferição do nível de desenvolvimento, de avaliação da personalidade, do estado emocional e do significado pessoal do tema retratado.[1-3]

A sua interpretação deve ser enquadrada no contexto clínico, integrada num plano de cuidados longitudinal e utilizada numa perspetiva evolutiva do desenvolvimento da criança. Deve ter em conta o estado de desenvolvimento em que se encontra a criança, os aspetos relacionais, familiares e sociais envolventes, a história clínica e o exame objetivo.[1-3] Não se pretende uma interpretação literal, mas antes uma orientação de hipóteses a serem exploradas de forma individualizada.

Numa vertente terapêutica, este recurso permite à criança expressar os seus desejos, medos e outros estados emocionais, facilitando a expressão e regulação emocional,[1-3] aspeto de particular importância em crianças com dificuldades de expressão verbal, como por exemplo crianças com perturbação do espetro do autismo,[4] ou com experiências traumáticas passadas.[1-3]

Ao permitir o acesso à vivência interna da criança, o desenho auxilia, também, a avaliação de abusos físicos, emocionais e sexuais.[5,6]

O Teste do Desenho da Família e o Teste da Figura Humana constituem dois exemplos de testes projetivos de inspiração psicodinâmica com muita utilidade na prática clínica.

Através do Teste do Desenho da Família é possível inferir como a criança interpreta o seu contexto familiar, que sentimentos nutre pelos elementos projetados e a posição em que se coloca na sua dinâmica familiar. Este teste pode ser efetuado dos cinco aos dezasseis anos e deve ter em conta a análise de três níveis – gráfico, estruturas formais e conteúdo.[3,7-9]

No nível gráfico, avalia-se a amplitude, a força e o ritmo do traço empregue no desenho, bem como a zona da página que ocupa e a direção em que é apresentado. Linhas traçadas num gesto amplo que ocupam uma boa parte da página sugerem energia e extroversão, ao passo que um traçado com linhas curtas sugere inibição. Um traço forte

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pode estar relacionado com agressividade, impulsividade e audácia ao invés de um traço fraco que pode sugerir fragilidade e timidez.[3,7-9]

No que respeita à zona da página ocupada pelo desenho, a escolha da zona inferior pode sugerir cansaço, astenia e depressão ao contrário da parte superior da página que pode remeter para imaginação e criatividade. A zona esquerda refere-se a tendências regressivas podendo sugerir passividade, falta de iniciativa e até mesmo uma forte dependência dos pais.[3,7-9] Por sua vez, a zona da direita corresponde ao desenvolvimento progressivo, capacidade de iniciativa e autonomia.[3,7-9] O sentido natural e progressivo do desenho efetua-se da esquerda para a direita, tal como o sentido da escrita e leitura, nos países ocidentais. Nos países de origem árabe e hebraica verifica-se ao contrário. Não se verificam diferenças na direção e na *performance* do desenho entre destros e canhotos.[10]

O nível da estrutura formal avalia a perfeição do desenho, traduzindo o grau de maturidade e o nível de desenvolvimento. A análise do conteúdo observa as tendências afetivas, que podem ser positivas, quando sentimentos de admiração ou de amor levam um sujeito a investir numa personagem privilegiada; ou negativas, quando sentimentos de desprezo ou ódio levam a que a criança desinvista numa personagem que é objeto de desvalorização no desenho.[7-9]

A personagem desenhada em primeiro lugar representa normalmente a pessoa mais valorizada e admirada pela criança, por quem esta nutre sentimentos mais fortes, mas também com quem esta se identifica. Posiciona-se num lugar de maior destaque, normalmente na posição inicial à esquerda da família, correspondendo habitualmente a um dos cuidadores. Normalmente, a criança desenha-se junto da pessoa mais significativa. A desvalorização de uma personagem expressa-se no desenho por omissão total da personagem ou de partes do corpo ou de detalhes da mesma, pela colocação em último lugar, na margem da página ou distanciada das outras personagens, implicando sentimentos negativos por essa pessoa. Se essa personagem for a própria criança pode sugerir fragilidades no ego, não se reconhecendo a si próprio como figura significativa daquele ambiente familiar.[7-9]

O desenho da família permite também aceder à forma como a criança, no seio da família, resolve o conflito da

Figura 1 – Desenho da família realizado por um menino seguido em consulta de Pedopsiquiatria por perturbação de hiperatividade e défice de atenção e perturbação de adaptação com sintomas ansiosos. Foi-lhe proposto que desenhasse uma família, tendo aderido com tranquilidade, apresentando-se calmo e com afetos positivos. Da esquerda para a direita: a criança em primeiro lugar, a mãe, o pai e a irmã mais nova. Em termos de desenvolvimento, o desenho inclui-se na fase do esquematismo, onde o esquema corporal da figura humana está mais definido, com maior proporção entre as partes do corpo e inclusão de vestimentas e ornamentos diferenciadores de género. Verifica-se investimento nas figuras humanas, sem omissão de partes do corpo, com proximidade entre todos os elementos, apresentando-os com fácies sorridente. O cuidador que desenha junto a si é a mãe, com quem terá a relação mais privilegiada, e que se infere ser a pessoa mais significativa do subsistema parental. A figura do pai parece desinvestida, ao surgir desenhada num tamanho inferior ao da própria criança. Através da restante avaliação da criança, percebeu-se que estava a vivenciar sentimentos intensos de rivalidade fraterna agudizados por uma situação de doença da irmã, que requeria mais atenção por parte da mãe. Estes sentimentos podem ser projetados no desenho, ao representar-se em primeiro lugar ao lado da mãe e num tamanho proporcionalmente maior em relação às restantes figuras, traduzindo a necessidade afetiva que poderia estar a vivenciar.

rivalidade fraterna e do conflito edipiano.[7-9] A distância entre as personagens reflete o modo como a criança encara essas relações. A aproximação entre duas pessoas sugere a proximidade vivida ou desejada pela criança, enquanto o distanciamento pode traduzir a dificuldade nessas relações familiares (Fig. 1).[7-9]

O Teste da Figura Humana auxilia a avaliação do nível cognitivo e a identificação de aspetos inconscientes e expressivos, traços de personalidade e experiências da criança com o outro e com o meio.[11] Constitui também um indicador de perturbações internalizantes, de identidade de género e do comportamento alimentar.[11,12]

A figura humana, na maioria das vezes, representa a própria criança ou as pessoas importantes à sua volta.[3,11,12]

Existem alguns indicadores no desenho da figura humana que podem revelar experiências de abuso físico ou sexual. A presença de partes do corpo exageradas ou realçadas, como mãos, ombros, nariz com narinas salientes, sobrancelhas, orelhas duplas ou salientes e a presença de dentes estão muitas vezes associadas a hostilidade e agressividade, e podem indiciar abuso físico.[5,6] Detalhes como olhos sombreados e a ausência de braços e mãos estão associados a sentimentos como desamparo, vergonha, medo e ansiedade social e encontram-se com maior frequência em crianças com vivências de abuso emocional. A presença de genitais excessivamente grandes ou sombreados, a ausência de características faciais, como por exemplo os olhos, a presença de detalhes como por exemplo um queixo duplo, braços ou pernas acentuadas ou ausentes, a omissão da parte inferior do corpo ou a flutuação da imagem no limbo, a nudez ou a representação de símbolos com forma fálica, podem sugerir abusos sexuais.[5,6] Contudo, há que interpretar estes desenhos de forma cuidada e contextualizada com a história de vida e a fase do desenvolvimento da criança. Nem sempre a manifestação de conteúdos, símbolos e temáticas erotizadas sugerem abusos sexuais, mas antes a curiosidade face à sexualidade própria da criança. Devem ser alvo de atenção os elementos hipersexualizados projetados nos desenhos manifestados de forma não isolada.[5,6,11,12]

Em conclusão, o desenho infantil, enquanto expressão do mundo interno da criança, permite aceder aos seus processos afetivos e cognitivos. Salienta-se a sua extrema importância na prática clínica pediátrica, constituindo um modo de comunicação, avaliação e intervenção facilmente disponível e naturalmente prazerosa.

CONTRIBUTO DOS AUTORES

Todos os autores contribuíram de igual forma para a conceptualização, pesquisa bibliográfica, escrita e revisão crítica do trabalho.

PROTECÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONSENTIMENTO DO DOENTE

Foram obtidos os respetivos consentimentos assinados pelos pais das crianças que realizaram os desenhos reproduzidos no artigo.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Family Satisfaction in Intensive Care during the COVID-19 Pandemic Using the FS-ICU24 Questionnaire

Satisfação dos Familiares em Cuidados Intensivos durante a Pandemia de COVID-19 Utilizando o Questionário FS-ICU24

ARTIGO ORIGINAL

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ABSTRACT

Introduction: The COVID-19 pandemic caused an abrupt change in the pattern of communication involving patients, family members, and healthcare professionals. This study aimed to evaluate family member satisfaction with intensive care units (ICU) care and communication strategies during the COVID-19 pandemic. Secondary objectives included identification of areas requiring improvement, and assessment of the impact of both COVID-19 diagnosis and in-person visits on overall satisfaction.

Material and Methods: A prospective, observational single-center study was conducted among family members of ICU patients admitted between March and September 2020. During this period, ICU visiting policies suffered changes, ranging from full restrictions to eased limitations, which impacted ICU communication procedures and patient contact with family members. Three months after ICU discharge, the designated family members of patients were contacted and invited to fill in a questionnaire that assessed family satisfaction using a Likert response scale.

Results: There was a total of 168 family members contacted (response rate of 57.7%). Most participants were globally satisfied with the care provided by the ICU staff and, apart from communication between nurses and family members, all other questions scored a satisfaction rate above 80%. The study found a statistically significant association between satisfaction and the consistency of clinical information provided and the possibility of having visits (p = 0.046). The odds ratio of being satisfied with information consistency was found to be 0.22 times lower in family members that were able to visit the patient in the ICU during the COVID-19 pandemic [OR = 0.22 (95% CI: 0.054 - 0.896)] compared with families that were unable to presential visit their family member. No statistically significant differences were found in the satisfaction rates between COVID-19 and non-COVID-19 admissions.

Conclusion: This is one of the first studies to assess satisfaction among family members of ICU patients during COVID-19 restrictions and the first, as far as we know, performed in the Portuguese population. The overall satisfaction levels were similar to the estimates found in previous studies. A lower degree of satisfaction with information consistency was found in family members who had in-person visits, possibly related with heterogeneity of senior doctors delivering information. COVID-19 diagnosis was not associated with decreased satisfaction.

Keywords: Communication; COVID-19; Intensive Care Units; Patient Satisfaction; Portugal; Quality of Health Care; Surveys and Questionnaires

RESUMO

Introdução: A pandemia de COVID-19 impôs alterações no padrão de comunicação entre doentes, familiares e profissionais. Os objectivos deste estudo foram avaliar a satisfação dos familiares com os cuidados prestados pelas unidades de cuidados intensivos e as estratégias comunicacionais durante a pandemia de COVID-19. Os objectivos secundários incluíram a identificação de áreas de melhoria e a avaliação do impacto do diagnóstico de COVID-19 e das visitas presenciais na satisfação global.

Material e Métodos: Estudo prospetivo, observacional e unicêntrico que avaliou os familiares de doentes em unidades de cuidados intensivos admitidos de março a setembro de 2020. Neste período, ocorreram alterações na política de visitas, que alternaram entre restrições totais e permissão de visitas restritas; estas modificações impuseram alterações na política de comunicação e no contacto dos doentes com os seus familiares. Aos três meses após alta da unidade de cuidados intensivos, o familiar de referência foi contactado para preencher um questionário que avaliou a sua satisfação através de uma escala de Likert.

Resultados: Cento e sessenta e oito familiares foram contactados (taxa de resposta de 57,7%). A maioria dos participantes estava globalmente satisfeita com os cuidados prestados e a generalidade das questões apresentava uma taxa de satisfação superior a 80%. Uma associação com significado estatístico foi encontrada entre a consistência da informação clínica e a possibilidade de visitas presenciais (p = 0,046). O *odds ratio* de satisfação foi 0,2 vezes menor em familiares que puderam visitar o doente durante a pandemia COVID-19 [OR = 0,22 (95% CI: 0,054 – 0,896)] em comparação com familiares cuja visita presencial não foi possível. O diagnóstico de COVID-19 não apresentou impacto na satisfação dos familiares.

Conclusão: Este é um dos primeiros estudos a avaliar a satisfação de familiares de doentes internados em unidades de cuidados intensivos durante a pandemia de COVID-19 e é, tanto quanto é do nosso conhecimento, o primeiro realizado numa população portuguesa. A satisfação global é semelhante a estudos prévios publicados. O menor grau de satisfação com a consistência da informação em familiares que fizeram visitas aos doentes pode estar relacionado com heterogeneidade no estilo de comunicação entre os médicos seniores da unidade de cuidados intensivos. O diagnóstico de COVID-19 não esteve associado a uma redução na satisfação global dos familiares.

Palavras-chave: Comunicação; COVID-19; Inquéritos e Questionários; Portugal; Qualidade dos Cuidados de Saúde; Satisfação do Doente; Unidades de Cuidados Intensivos

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INTRODUCTION

In recent years, Intensive Care Medicine shifted from patient centered care to patient and family centered care.[1,2] Consequently, the perceived quality of care by patients and family members has become an area of special interest with multiple strategies to leverage knowledge and continuous improvement.[3] Among different interventions, a proactive communication is recognized to play a key role.[4,5] Therefore, assessment of family member satisfaction is a valuable tool in the global process of quality improvement in intensive care units (ICU),[2] namely quality of the communication process. Questionnaires comprise one of the several methods used to assess family member satisfaction in the ICU. In a recent systematic review, "Family Satisfaction in the Intensive Care Unit" (FS-ICU24) questionnaire was identified as one of the most reliable in terms of psychometric properties.[3]

The outbreak of the new coronavirus disease (COVID-19) brought on a pandemic crisis that affected almost every country in the world, with more than 250 million confirmed cases in a two-year period.[6] Its rapid growth led to an overwhelming pressure in hospital and ICU settings.[7] Faced with the rapid spread of COVID-19, social distancing measures and social isolation became mandatory in most European countries, and Portugal was no exception.[8-10] This health crisis caused a dramatic and abrupt change in the pattern of communication involving all parties, with a particular impact on patients and their family members, mainly in the ICU setting, with loss of non-verbal communication cues such as voice tone, posture, or face expression. Effective communication is known to rely on both verbal and non-verbal dimensions, with the latter being more significantly disrupted by the physical barriers imposed by the pandemic.[4] Different tools have been developed to minimize the physical distance impacting patients and their loved ones[11] and several recommendations have been made on how to overcome isolation.[12]

The aim of this study was to assess family member satisfaction with ICU care and communication strategies during the COVID-19 pandemic. Secondary objectives included identification of improvement areas, and assessment of the impact of both COVID-19 diagnosis and face-to-face visits in the overall satisfaction level.

MATERIAL AND METHODS

Setting

A prospective observational study was conducted among families of ICU patients admitted between March and September 2020 in a 21-bed single center ICU, at a district hospital in northern Portugal. The pre-pandemic ICU policy included a liberal daily visiting period (11 am to 8 pm), where family members could visit their relatives and access clinical updates from the senior doctor in charge. Due to the COVID-19 pandemic and in accordance with local and government policies, full restrictions of hospital visits were applied between March and June 2020. Since June 2020, local policies have allowed a short visiting period for ICU patients.

Several strategies were developed to reduce the gap between patients and family members due to the implemented restrictions, with the additional need to address both the virtual clinical updates and the family expectations. Following a literature review of previous reports, mainly from the first epidemic center in Europe,[13] the ICU unit implemented several changes to the patient-communication policy. This included a daily videoconference call to all eligible patients (awake and able to interact), identified in the morning shift using a checklist, which addressed current and target Richmond Agitation-Sedation Scale (RASS) scores, delirium and competence to interact with the environment. Clinical updates were given by telephone daily by one of the senior intensivists. On weekdays, this task was carried out by the same intensivist, in order to ensure consistency of information. On weekends, this responsibility was assigned to the most experienced doctor on duty. These clinical updates were addressed to a designated family member, over 18 years old.

Population

Three months after discharge from the ICU, designated family members of patients were contacted by telephone and were invited to participate in the survey. Informed consent was obtained and an email with an anonymous online questionnaire was sent. This included a formal written consent form, questions concerning the demographic profile and the FS-ICU24 questionnaire. Full anonymity and confidentiality were assured, and measures to guarantee confidentiality were put in place. Data was aggregated at the end of the study and statistical analyses were conducted.

The inclusion criteria were: patient's designated family member, as defined upon ICU admission by patient and clinical staff. The study considered all admissions between March and September 2020.

The exclusion criteria were: family members of patients with an ICU hospitalization period under 48 hours (to ensure sufficient exposure to ICU routines) and family members of patients who died during hospitalization.

Ethics Committee

The full study protocol was approved by the local Ethics Committee (Comissão de Ética para a Saúde da ULSM, E.P.E.) under identification number 54/CE/JAS.

Questionnaire

An online form of the FS-ICU24,[14] translated and validated to Portuguese language,[15] was adapted to the present study. The FS-ICU24 is a 24-question tool that assesses family satisfaction using a contained Likert response scale ranging from "very dissatisfied" to "completely satisfied" regarding satisfaction in two major subsets: satisfaction with information and satisfaction with the decision-making process. Several questions of the FS-ICU24 cover specific content regarding physical interaction, such as symptom

management, coordination of care, waiting room atmosphere and participation in daily rounds. Since physical and direct contact with the designated family member was not possible during the study period, these questions were previously excluded.

Statistical analysis

A descriptive analysis of collected data was conducted. Categorical variables are presented as frequencies and percentages, whereas the continuous variable is expressed as mean and standard deviation. Normal distribution was verified using skewness and kurtosis (accepted values between -1 and +1). In order to create a binary variable, family satisfaction with each item of the FS-ICU24 questionnaire was categorized into globally satisfied ("completely satisfied" and "very satisfied" responses) or globally unsatisfied ("mostly satisfied", "slightly dissatisfied" and "very dissatisfied" responses), as determined by previous manuscripts.[2]

Comparison tests were used to test for an association between the family's global satisfaction and their individual characteristics. Continuous variables were compared using independent-sample *t*-test and categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, depending on sample size.

All reported *p* values are two-tailed, with a *p* value < 0.05 indicating statistical significance. Analyses were performed using Statistical Package for Social Sciences (SPSS) software (version 27).

RESULTS

During the study period, 266 patients were admitted to the ICU, of whom 64 died during hospitalization (51 in the ICU and 13 in the general ward), thus excluding family members from the survey. Additionally, 11 patients had an ICU hospitalization under 48 hours and their families were consequently excluded. Another 20 families were not included in the study due to the inability to attain a formal contact (after two missed phone calls in a 24-hour period), and three refused to participate. Questionnaires were sent to 168 relatives, with a response rate of 57.7%.

Characteristics of participants and responses

The mean age of family members was 52.2 years [standard deviation (SD) = 13] and the majority was female

Table 1 – Demographic characteristics of responders

Age (years), mean ± sd	52.2	± 13
Sex, n (%)		
Female	67	(69.1)
Male	30	(31.9)
Kinship, n (%)		
Spouse	48	(49.5)
Son / daughter	33	(34.0)
Parent	9	(9.3)
Other	7	(7.2)
Frequency of contact with patient, n (%)		
Daily	61	(62.8)
More than once a week	15	(15.4)
Weekly	13	(13.4)
Monthly	8	(8.2)
Shares residence with patient, n (%)		
Yes	61	(62.8)
No	36	(37.1)
Resides in the same locality of the hospital, n (%)		
Yes	47	(48.5)
No	50	(51.5)
Educational level, n (%)*		
Less than basic education	17	(17.7)
Basic education	14	(14.6)
Secondary education (not completed)	15	(15.6)
Secondary education (completed)	28	(29.2)
Technical course	6	(6.3)
Bachelor degree	16	(16.7)

n: number of relatives; sd: standard deviation.
*: 1 missing value for education level

(69%). The most frequent kinship was spouse (48%), and most family members reported a daily contact with the patient (61%). More than half of the interviewed (51.6%) had completed secondary education (Table 1).

Most participants were globally satisfied (defined as being "very satisfied" or "completely satisfied") with the care provided by the ICU staff (Table 2). Apart from communication between nurses and family members, all other questions scored a percentage of global satisfaction above 80%.

During the study period, 34% of patients were admitted due to COVID-19 pneumonia and 58% of their family members were also diagnosed with SARS-CoV-2 infection. To assess the impact of the COVID-19-related hospitalization on family satisfaction, comparison tests were performed, and no statistically significant differences were found among satisfaction rates between COVID-19 and non-COVID-19 related admissions (Table 3).

During the study period, restrictions to visits related with the pandemic were eased, which allowed 40.2% of family members to visit patients during their ICU hospitalization. To assess the impact of in-person visits during ICU hospitalization on family satisfaction, comparison tests were performed. A statistically significant association was found between satisfaction and the consistency of clinical information provided and the possibility of having in-person visits (p = 0.046). The odds ratio of being satisfied with information consistency was found to be 0.22 times lower in family members who were able to visit the patient in the ICU during the COVID-19 pandemic [OR = 0.22 (95% CI: 0.054 - 0.896)] (Table 4).

DISCUSSION

To the best of our knowledge, this is one of the first studies to assess satisfaction among family members of ICU patients during COVID-19 restrictions and the first performed among the Portuguese population. There are several methods that can be used to acquire family satisfaction assessments, with questionnaires being one of the most common and replicable in literature.[2,3,14,16,17]

In this study, overall satisfaction stood mostly above 80%, which is consistent with previous studies published in the literature.[2,18] In this ICU, communication with families is mainly done by doctors, which can justify the lower satisfaction levels of respondents regarding communication with nurses.

Approximately 60% of families were not allowed to be present during ICU hospitalizations. Consequently, several items in the FS-ICU24 questionnaire were interpreted through telephone experiences and video calls, namely sections concerning decision-making processes and the care provided to the patient. Surprisingly, statistical significance was found between satisfaction with information consistency and in-person visits, with an odds ratio of 0.22 disfavoring in-person visits. As previously noted, for families that were unable to visit their relatives at the hospital, daily communication was carried out by a single senior doctor; for those who were able to visit, this communication was

Table 2 – Responses to FS-ICU 24

Items	Very dissatisfied		Slightly dissatisfied		Mostly satisfied		Very satisfied		Completely satisfied		Non applicable		Globally satisfied*	
How well the ICU staff showed an interest in your needs, n (%)	0	(0.0)	0	(0.0)	12	(12.4)	28	(28.9)	57	(58.8)	0	(0.0)	85	(87.6)
How well the ICU staff provided emotional support to you, n (%)	0	(0.0)	0	(0.0)	15	(15.5)	29	(29.9)	52	(53.6)	1	(1.0)	81	(83.5)
The courtesy, respect, and compassion you were given, n (%)	0	(0.0)	0	(0.0)	17	(17.5)	30	(30.9)	49	(50.5)	1	(1.0)	79	(81.4)
How often nurses communicated to you about your family member's condition, n (%)	3	(3.1)	4	(4.1)	11	(11.3)	24	(24.7)	34	(35.1)	21	(21.7)	59	(60.8)
How often doctors communicated to you about your family member's condition, n (%)	0	(0.0)	2	(2.1)	13	(13.4)	26	(26.8)	52	(53.6)	4	(4.1)	78	(80.4)
Willingness of ICU staff to answer your questions, n (%)	1	(1.0)	1	(1.0)	9	(9.3)	30	(30.9)	54	(55.7)	2	(2.1)	84	(86.6)
How well ICU staff provided you with explanations that you understood, n (%)	1	(1.0)	1	(1.0)	10	(10.3)	32	(33.0)	51	(52.6)	2	(2.1)	83	(85.6)
The honesty of information provided to you about your family member's condition, n (%)	0	(0.0)	2	(2.1)	5	(5.2)	34	(35.1)	55	(56.7)	1	(1.0)	89	(91.8)
How well ICU staff informed you what was happening to your family member and why things were being done, n (%)	0	(0.0)	2	(2.1)	9	(9.3)	36	(37.1)	48	(49.5)	2	(2.1)	84	(86.6)
The consistency of information provided to you about your family member's condition, n (%)	2	(2.1)	1	(1.0)	8	(8.2)	34	(35.1)	47	(48.5)	5	(5.2)	81	(83.5)

n: number of responses
*: globally satisfied defined as being very or completely satisfied

Table 3 – Comparison between COVID-19 and non-COVID-19 admissions regarding global satisfaction (FS-ICU 24)

Items	COVID-19				non COVID-19				OR (95% CI)		p value
	Globally satisfied*		Non satisfied		Globally satisfied*		Non satisfied				
How well the ICU staff showed an interest in your needs, n (%)	27	(81.8)	6	(18.2)	58	(90.6)	6	(9.4)	0.47	(0.14 - 1.58)	0.328[2]
How well the ICU staff provided emotional support to you, n (%)	27	(81.8)	6	(18.2)	54	(85.7)	9	(14.3)	0.75	(0.24 - 2.33)	0.618[1]
The courtesy, respect, and compassion you were given, n (%)	27	(81.8)	6	(18.2)	52	(82.5)	11	(17.5)	0.95	(0.32 - 2.85)	0.930[1]
How often nurses communicated to you about your family member's condition, n (%)	13	(72.2)	5	(27.8)	46	(79.3)	12	(20.7)	0.68	(0.20 - 2.28)	0.531[2]
How often doctors communicated to you about your family member's condition, n (%)	26	(81.3)	6	(18.8)	52	(85.2)	9	(14.8)	0.75	(0.24 - 2.33)	0.619[1]
Willingness of ICU staff to answer your questions, n (%)	30	(90.9)	3	(9.1)	54	(87.1)	8	(12.9)	1.48	(0.37 - 6.01)	0.742[2]
How well ICU staff provided you with explanations that you understood, n (%)	30	(90.9)	3	(9.1)	53	(85.5)	9	(14.5)	1.70	(0.43 - 6.76)	0.533[2]
The honesty of information provided to you about your family member's condition, n (%)	30	(90.9)	3	(9.1)	59	(97.7)	4	(6.3)	0.68	(0.14 - 3.23)	0.689[2]
How well ICU staff informed you what was happening to your family member and why things were being done, n (%)	30	(90.9)	3	(9.1)	54	(87.1)	8	(12.9)	1.48	(0.37 - 6.01)	0.742[2]
The consistency of information provided to you about your family member's condition, n (%)	27	(90)	3	(10)	54	(87.1)	8	(12.9)	1.33	(0.33 - 5.43)	1.000[2]

n: number of responses
*: globally satisfied defined as being very or completely satisfied
[1]: Pearson's chi square test; [2]: Fisher's exact test

Table 4 – Comparison between in-person and non in-person visits regarding global satisfaction (FS-ICU 24)

Items	Presencial visits				No presential visits				OR (95% CI)		p value
	Globally satisfied*		Non satisfied		Globally satisfied*		Non satisfied				
How well the ICU staff showed an interest in your needs, n (%)	35	(89.7)	4	(10.3)	50	(86.2)	8	(13.8)	1.40	(0.39 - 5.01)	0.757[2]
How well the ICU staff provided emotional support to you, n (%)	34	(87.2)	5	(12.8)	47	(82.5)	10	(17.5)	1.45	(0.45 - 4.61)	0.531[1]
The courtesy, respect, and compassion you were given, n (%)	33	(8.6)	6	(15.4)	46	(80.7)	11	(19.3)	1.32	(0.44 - 3.91)	0.622[1]
How often nurses communicated to you about your family member's condition, n (%)	27	(75.0)	9	(25.0)	32	(80.0)	8	(20.0)	0.75	(0.25 - 2.21)	0.601[1]
How often doctors communicated to you about your family member's condition, n (%)	30	(78.9)	8	(21.1)	48	(87.3)	7	(12.7)	0.55	(0.18 - 1.66)	0.283[1]
Willingness of ICU staff to answer your questions, n (%)	34	(89.5)	4	(10.5)	50	(87.7)	7	(12.3)	1.19	(0.32 - 4.38)	1.000[2]
How well ICU staff provided you with explanations that you understood, n (%)	31	(81.6)	7	(18.4)	52	(91.2)	5	(8.8)	0.43	(0.12 - 1.46)	0.212[2]
The honesty of information provided to you about your family member's condition, n (%)	35	(89.7)	4	(10.3)	54	(94.7)	3	(5.3)	0.49	(0.10 - 2.31)	0.437[2]
How well ICU staff informed you what was happening to your family member and why things were being done, n (%)	33	(86.8)	5	(13.2)	51	(89.5)	6	(10.5)	0.78	(0.22 - 2.75)	0.750[2]
The consistency of information provided to you about your family member's condition, n (%)	30	(78.9)	8	(21.1)	51	(94.4)	3	(5.6)	**0.22**	**(0.05 - 0.90)**	**0.046**[2]

n: number of responses
*: globally satisfied defined as being very or completely satisfied
[1]: Pearson's chi square test; [2]: Fisher's exact test

done in-person by the patient's assigned doctor. This heterogeneity of interlocutors may justify the statistical difference regarding information consistency and highlights its importance throughout the entire ICU hospitalization experience.

A COVID-19 diagnosis has a psychological impact on various domains, not only on healthcare workers[12,19] but also on family-patient close interactions, which were inevitably disrupted.[12,20] The role of family members of ICU patients goes beyond legal and informative aspects: they serve as advocates for the patients' wishes and informants for significant others who cannot be physically or virtually connected to the patient.[4,11,21] Concerns of death among loved ones, severe course of illness, healthcare failure and general social and economic changes have been reported, with decreased levels of happiness and overall life satisfaction, which in turn can predispose to depression and anxiety.[22] This problem was already assessed in the COVID-19 pandemic by Cattelan and colleagues,[23] where the designated family members experienced psychological distress and reported remote communication as an overall negative experience.

This study hypothesized that general satisfaction could be lower, if COVID-19 disease was the major cause of admission in the ICU. However, during the course of the study, there were no statistically significant differences found in overall satisfaction between families whose relatives were admitted due to COVID-19 pneumonia and those who were not. It is possible that concerns about ICU hospitalization itself may supersede the specific diagnosis. More research is needed to assess the specific impact of a COVID-19 pneumonia diagnosis on family satisfaction.

In addition, areas of improvement were also identified, mainly through open questions at the end of the survey. Family members of 26 patients suggested several changes to our current policy, such as more than one daily communication with the ICU team or more time spent during visiting hours. Their suggestions are currently being reviewed in order to assess their feasibility in the future.

This study had several limitations. Families of patients who died in the ICU were excluded to avoid imposing a telephone conversation during a recent mourning. Nonetheless, there are previous studies reporting higher satisfaction rates in family members of patients who died in the ICU, compared with survivors.[17,18] Although bias may be present, the responses of these families would probably sustain or increase the overall satisfaction rates. Although our study sample is smaller compared to other published studies,[18] single and multicenter studies were found with similar number of respondents.[2, 24] The population interviewed in this single center survey was mainly made up of female spouses. Even though this reflects the real demography of the population under study, specific variations in other relevant subgroups may differ from this reality, as previous studies found that white ethnicity had a higher satisfaction rates compared with members of other ethnicities.[14] The response rate was only 57.7%, which might be a potential respondent bias in survey-dependent studies; however, this response rate is identical to others in the literature.[17,18] The FS-ICU24 is a questionnaire that assesses patients' family satisfaction with ICU provided care[14,15] and was found to be one of the most reliable and valid in relation to its psychometric properties.[3] Nevertheless, care must be taken in conclusions obtained from a single research method.

CONCLUSION

This is one of the first studies to assess satisfaction among family members of ICU patients during COVID-19 restrictions and the first performed within the Portuguese population. Overall satisfaction levels were similar to estimates found in previous studies. A lower degree of satisfaction with information consistency was found in family members who had in-person visits, possibly related with the heterogeneity of senior doctors delivering information. A COVID-19 diagnosis was not associated with decreased satisfaction.

AUTHOR CONTRIBUTIONS

JC: design of the work, data acquisition, drafting of the paper.

CTL: data acquisition and analysis, drafting of the paper.

DC, EG: statistics and critical review.

RA: critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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Tradução, Adaptação Cultural e Contributos para a Validação da Escala Nijmegen Cochlear Implant Questionnaire (NCIQ) para o Português Europeu

Translation, Cultural Adaptation and Contributions to the Validation of the Nijmegen Cochlear Implant Questionnaire (NCIQ) for European Portuguese

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RESUMO

Introdução: O questionário *Nijmegen Cochlear Implant Questionnaire* (NCIQ) consiste numa escala simples e de rápida aplicação para avaliar a satisfação dos indivíduos que utilizam implantes cocleares. O objetivo deste estudo foi a validação do NCIQ para o Português Europeu e avaliação da qualidade de vida em adultos utilizadores de implantes cocleares.

Material e Métodos: Participaram no estudo 50 adultos utilizadores de implante coclear multicanal (uni ou bilateral), com surdez pós-lingual, no mínimo com 12 meses de uso, implantados e seguidos no serviço de Otorrinolaringologia do Hospital Egas Moniz em Lisboa. Foram pedidas a autorização e as normas para a tradução do questionário aos autores da escala e realizada a tradução e retroversão do questionário, a adaptação cultural, e a avaliação da reprodutibilidade e da consistência interna.

Resultados: Os participantes eram 44,0% do género masculino e 56,0% do feminino, com idades compreendidas entre os 20 e os 79 anos (55,50 ± 15,69). Os resultados obtidos neste estudo demonstraram um nível de satisfação global de 65,07 nos utilizadores de implantes cocleares. O nível de satisfação dos subdomínios foi de 64,40 na perceção básica do som, 71,35 na perceção avançada do som, 57,91 na produção da fala, 59,05 na autoestima, 69,75 na atividade e 68,50 nas interações sociais. A versão traduzida do questionário NCIQ apresentou uma boa consistência interna para todos os domínios existentes no questionário (α de Cronbach = 0,96). Verificou-se também uma boa reprodutibilidade inter-pesquisadores. Para a pontuação global e das subescalas do questionário, os resultados médios obtidos demonstraram não haver diferenças significativas com a escala original.

Conclusão: A adaptação do *Nijmegen Cochlear Implant Questionnaire* para Português Europeu deve ser considerada um bom instrumento para a avaliação da satisfação dos utilizadores de implantes cocleares e é, até ao momento, a única escala neste domínio validada para aplicação na população portuguesa.

Palavras-chave: Implante Coclear; Implantes Cocleares; Inquéritos e Questionários; Percepção da Fala; Portugal; Qualidade de Vida; Reprodutibilidade dos Testes; Tradução

ABSTRACT

Introduction: The Nijmegen Cochlear Implant Questionnaire (NCIQ) scale uses a simple and easily administered questionnaire to evaluate the adaptation of individuals to their cochlear implants. The aim of this study was to validate the NCIQ for European Portuguese, through its translation and cultural adaptation. It also presents the evaluation of reproducibility and the description of the results of this questionnaire in patients using IC.

Material and Methods: Fifty postlingually deaf adult multichannel cochlear implant users (uni- or bilateral) participated in the study. Participants used the cochlear implant for at least 12 months and were patients of the Department of Otolaryngology at the Egas Moniz Hospital in Lisbon. Permission, as well the guidelines for translation, were obtained from the authors of the scale. Translation and cultural adaptation were carried out, in addition to the evaluation of reproducibility and internal consistency.

Results: The participants were 44.0% male and 56.0% female, aged between 20 and 79 years (55.50 ± 15.69). The results of the study showed an overall level of satisfaction of 65.07 among cochlear implants users. The level of satisfaction of the subdomains was 64.40 in basic sound perception, 71.35 in advanced sound perception, 57.91 in speech production, 59.05 in self-esteem, 69.75 in activity and 68.50 in social functioning. Internal consistency (Cronbach α score = 0.96) and test-retest reliability coefficients proved to be strong. Furthermore, the questionnaire's overall and subdomains average scores did not differ significantly from the results obtained with the original scale.

Conclusion: This adaptation of the NCIQ questionnaire for European Portuguese should be considered a good tool to evaluate the level of satisfaction of cochlear implant users and, so far, it is the only scale in this field validated for application in the Portuguese population.

Keywords: Cochlear Implantation; Cochlear Implants; Portugal; Quality of Life; Reproducibility of Results; Speech Perception; Surveys and Questionnaires; Translation

INTRODUÇÃO

O implante coclear (IC) é um dispositivo capaz de transformar os sons e ruídos ambientes em energia elétrica e de os conduzir ao nervo coclear, de forma a gerar uma sensação auditiva.[1] A implantação coclear é atualmente um

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tratamento de rotina recomendado para indivíduos com surdez de grau profundo ou para indivíduos com surdez de grau severo que não beneficiem ou tenham um benefício mínimo com prótese auditiva, desde que se tenha confirmado por meios imagiológicos que a inserção dos elétrodos na cóclea é viável, que existe nervo auditivo e que não existem riscos de não adesão ao plano de tratamento e reabilitação.[2-8]

A maior parte dos estudos que avaliam a eficácia dos IC centra-se na quantificação do ganho funcional audiológico ou do reconhecimento da fala.[9] Poucos estudos realizados se têm centrado nas medidas de avaliação da satisfação ou da qualidade de vida por parte dos doentes utilizadores de IC.[10] Os resultados destes estudos, realizados para avaliar a satisfação ou a qualidade de vida dos doentes com IC, não têm demonstrado uma correlação significativa com os estudos que avaliam os resultados audiológicos,[11-14] sugerindo que a avaliação do ganho funcional ou do reconhecimento da fala não é suficiente para avaliar e quantificar os benefícios da implantação coclear.[15]

Diversos instrumentos têm sido utilizados para avaliar o nível de satisfação dos indivíduos que utilizam IC.[16] Habitualmente são utilizadas escalas que apreciam diversos aspetos relacionados com a sua utilização, mas muitas destas escalas são genéricas, não desenhadas especificamente para avaliar doentes com IC e sem a sensibilidade ou adequação suficientes para recolher alguns dos aspetos que são particulares aos doentes que utilizam IC.[11,15,17,18]

A escala *Nijmegen Cochlear Implant Questionnaire* (NCIQ)[11] é uma escala específica para doentes com IC, ainda não validada para o Português Europeu, e tem vindo a ser reconhecida como a escala mais ajustada para avaliar a qualidade de vida nos doentes com IC.[19-22] É assim de todo o interesse a disponibilidade de uma escala desenhada especificamente para avaliar a satisfação e qualidade de vida nos doentes com IC e validada para a língua Portuguesa Europeia, possibilitando a comparação dos resultados dos estudos portugueses com os estudos internacionais.

O presente trabalho teve como objetivo a validação do NCIQ para a língua Portuguesa Europeia, que incluiu diversas etapas: tradução, adaptação cultural, avaliação da reprodutibilidade e descrição dos resultados da aplicação deste questionário em pacientes adaptados com IC.

MATERIAL E MÉTODOS

Este estudo foi aprovado pela Comissão de Ética para a Saúde (CES) do Centro Hospitalar de Lisboa Ocidental (CHLO), em Lisboa, a 8 de Janeiro de 2020, tendo sido atribuído o n.º 20170700050 no Registo Nacional de Estudos Clínicos (RNEC). O estudo foi conduzido segundo os princípios da Declaração de Helsínquia actualizada em 2013. Os indivíduos, maiores de idade e que concordaram em participar no estudo, assinaram o termo de consentimento informado.

Foi utilizada uma amostra de conveniência que incluiu 50 utentes implantados e seguidos no serviço de Otorrinolaringologia do Hospital Egas Moniz do CHLO, com idade entre os 20 e 79 anos e de ambos os géneros. Os participantes preencheram os seguintes critérios de inclusão: perda auditiva pós-lingual, surdez bilateral (não necessariamente simétrica), adaptação com IC (uni ou bilateral), no mínimo 12 meses de implantação e uso (para o cálculo do tempo de uso do IC foi considerada a data da ativação do dispositivo), capacidade de compreensão e leitura da língua portuguesa suficiente para responder a todas as subescalas do NCIQ. Foram excluídos do estudo os indivíduos que apresentaram grave limitação da capacidade de compreensão e expressão para responder.

Foi pedida autorização aos autores do NCIQ original para a sua adaptação e validação para Português Europeu. Esta autorização foi concedida a 12/09/2019 pelos autores do questionário pertencentes à Universidade de Nijmegen[11] e seguiu-se a técnica proposta pela Scientific Advisory Committee of Medical Outcomes Trust.[23]

Na fase de adaptação cultural e teste da reprodutibilidade os questionários foram respondidos por 21 voluntários. Na fase de validação, 41 utilizadores de IC foram contactados telefonicamente e convidados a responder por correio. Destes, 29 voluntários responderam ao questionário NCIQ Português Europeu na íntegra. O grupo de voluntários do estudo constitui um total de 50 indivíduos.

Procedimentos

A - Tradução do idioma inglês para o português e adaptação linguística

Distribuição do questionário por dois tradutores de inglês, fluentes nesse idioma, que não se conheciam e que não tinham visto previamente o questionário. O objetivo foi criar duas traduções independentes do NCIQ.

B - Revisão da tradução para português por grupo de revisão

Constituição dum grupo de revisão composto por três profissionais bilingues (portugueses, conhecedores com fluência do inglês) na área da Otorrinolaringologia e Audiologia, que analisaram os dois documentos resultantes. Por consenso, reduziram as diferenças encontradas nas traduções, escolhendo as melhores expressões e palavras para cada questão, e adaptaram o texto ao conhecimento cultural português. Obteve-se um novo e único questionário que se denominou NCIQ Português Europeu.

C - Retroversão da tradução

Uma cópia do NCIQ Português Europeu obtido foi encaminhada para outros dois tradutores de inglês, desconhecedores do texto original e do estudo, bem como dos tradutores iniciais, para evitar qualquer influência na tradução. Estes realizaram a retroversão da tradução, e o mesmo grupo revisor reavaliou a versão resultante, comparando-a com a original em inglês.

D - Adaptação cultural

A adaptação cultural do NCIQ Português Europeu teve como objetivo estabelecer a equivalência cultural entre as

versões inglesa e portuguesa do questionário. Os questionários dos primeiros 21 doentes foram utilizados para o estudo da adaptação cultural e reprodutibilidade. Um primeiro entrevistador (entrevistador 1) aplicou o questionário, lendo oralmente cada questão que suscitasse dúvidas, a fim de localizar eventuais dúvidas que surgissem na interpretação das perguntas do questionário. De acordo com Guillemin *et al*,[24] a equivalência cultural é estabelecida quando no mínimo 80% dos indivíduos não mostram qualquer tipo de dificuldade em compreender e responder a cada questão formulada. Caso o valor seja menor que este limite, então essa questão será submetida individualmente a um novo processo de tradução. A versão do NCIQ Português Europeu foi aplicada aos indivíduos nesta fase e respondida na sua totalidade, não tendo sido encontradas dificuldades na compreensão das questões.

E- Reprodutibilidade do questionário

Para testar a reprodutibilidade inter-pesquisadores, o questionário foi aplicado aos mesmos 21 pacientes entrevistados na fase de adaptação cultural por um segundo entrevistador (entrevistador 2), sendo que a aplicação do teste-reteste ocorreu geralmente entre duas consultas espaçadas um mês entre si. A comparação dos resultados do questionário realizado por entrevistadores diferentes foi usada para avaliação da reprodutibilidade inter-pesquisadores.

Pontuação

O NCIQ é um questionário específico para a avaliação da qualidade de vida em adultos utilizadores de IC. É constituído por 60 perguntas divididas em três domínios gerais, com os seus respetivos subdomínios: físico (perceção básica do som, perceção avançada do som e produção da fala), psicológico (autoestima) e social (limitações às atividades e interações sociais)[11] (Tabela 1).

O NCIQ é estruturado em 10 perguntas para cada subdomínio. Cada pergunta apresenta cinco alternativas de resposta, sendo que nas 55 primeiras perguntas as respostas possíveis são: 1 = "nunca"; 2 = "às vezes"; 3 = "habitualmente"; 4 = "quase sempre"; e 5 = "sempre". As cinco perguntas finais possuem as respostas 1 = "não"; 2 = "mau"; 3 = "razoável"; 4 = "bom"; e 5 = "excelente". Para todas as 60 perguntas existe ainda uma sexta opção de resposta, caso a pergunta não seja considerada pertinente às condições do indivíduo ("não aplicável" ou "N/A"). No mínimo, sete das dez perguntas devem ser respondidas para concluir cada subdomínio. As respostas são pontuadas de tal forma que a satisfação seja refletida por uma maior pontuação (de 0 a 100). A pontuação para cada resposta em subdomínio é atribuída da seguinte forma: 1 = 0, 2 = 25, 3 = 50, 4 = 75 e 5 = 100. Existe uma recodificação inversa da pontuação das respostas referidas no livro de códigos da tabela final do questionário, ou seja, nestes casos a resposta 1 expressa maior satisfação (1 = 100, 2 = 75, 3 = 50, 4 = 25 e 5 = 0). Depois de finalizada a soma de todas as perguntas de um subdomínio, divide-se o valor total pelo número de respostas completas. Também é gerada uma pontuação para cada um dos domínios.

O questionário foi inicialmente concebido de forma a que o próprio doente assinalasse as respostas, com caneta e papel, conforme sugerido pelos autores da escala. Contudo, na fase de estudo da adaptação cultural e reprodutibilidade inter-pesquisadores e para evitar dificuldades na resposta ao questionário, optou-se pelo formato de entrevista, com leitura em voz alta e anotação das respostas, o que possibilitou uma melhor compreensão das questões e das alternativas de resposta.

Métodos estatísticos

Os dados recolhidos foram introduzidos numa base de dados, sendo o estudo estatístico realizado com recurso ao *Statistical Package for The Social Sciences* (SPSS)® versão 20.0 para Windows.

Para a análise das diversas variáveis do estudo, foi utilizada uma análise estatística descritiva com a obtenção dos resultados da média, valor mínimo, valor máximo e desvio padrão para cada pergunta do questionário. Realizou-se a análise da reprodutibilidade com o coeficiente de correlação interclasses (após confirmação de que os dados seguiam a distribuição normal). Foi igualmente realizada a avaliação da consistência interna do NCIQ através do α de Cronbach para os domínios e subdomínios do NCIQ. Este coeficiente é uma ferramenta estatística que quantifica a confiabilidade de um questionário numa escala de 0 a 1. O valor mínimo aceitável para se considerar um questionário confiável é de 0,7.[25] Por fim, realizou-se a comparação dos níveis de satisfação obtidos com os da amostra holandesa (Hinderink *et al*).[11] O nível de significância adotado para os testes estatísticos foi de 0,05.

Tabela 1 – Domínios e subdomínios do questionário NCIQ

Domínio	Subdomínio	Perguntas	Pontuação por resposta
Físico	Perceção básica do som	1, 7, 13, 19, 25, 31, 37, 42, 47, 52	1 = 0 2 = 25 3 = 50 4 = 75 5 = 100
	Perceção avançada do som	5, 11, 17, 23, 29, 35, 40, 45, 50, 60	
	Produção da fala	3, 9, 15, 21, 27, 33, 56, 57, 58, 59	
Psicológico	Autoestima	4, 10, 16, 22, 28, 34, 39, 44, 49, 54	
Social	Limitações às atividades	6, 12, 18, 24, 30, 36, 41, 46, 51, 55	
	Interações sociais	2, 8, 14, 20, 26, 32, 38, 43, 48,53	

Recodificação: 50, 27, 10, 16, 22, 34, 39, 49, 54, 6, 12, 18, 24, 30, 36, 41, 46, 51, 55, 2, 8, 14, 20, 26, 38, 43, 48, 53.

RESULTADOS

Participaram no estudo 50 indivíduos adaptados com IC. A média de idades foi de 55,50 anos (desvio-padrão de 15,69), tendo o indivíduo mais jovem 20 anos e o mais velho 79 anos (Tabela 2). No que se refere ao género, a divisão dos indivíduos mostrou-se equilibrada, com discreto predomínio do género feminino (56%). O tempo de uso do implante coclear foi, em média, de 58,62 meses, variando entre os 14 e os 216 meses. A mediana foi de 40,00 com quartis Q1 = 27,00 e Q3 = 75,00, com um mínimo de 14,00 e um máximo de 216,00 A duração média diária de uso do implante foi de mais de nove horas em 70% dos indivíduos e mais de 13 horas em 40%. A origem hereditária foi a causa identificável de surdez mais frequente que conduziu à implantação.

A Tabela 3 apresenta uma análise descritiva dos resultados para cada domínio e subdomínio do questionário, baseados nas respostas da amostra de 50 indivíduos. Do grupo inicial de 21 indivíduos foram consideradas as respostas do avaliador principal (entrevistador 1), pois a comparação para cada questão entre a primeira e segunda aplicação do questionário não apresentou diferenças estatisticamente significativas. Os participantes deste estudo demonstraram maior satisfação para o domínio perceção avançada do som (M = 71,35; DP = 20,22) e no subdomínio limitação às atividades (M = 69,75; DP = 21,26): no domínio produção da fala a satisfação foi menor (M = 57,91; DP = 22,10), o mesmo acontecendo no subdomínio da autoestima (M = 59,05; DP = 15,23) (Fig. 1). O posicionamento dos domínios em relação à satisfação global (M = 65,07; DP = 16,21) dos utilizadores de IC foi a seguinte: os domínios perceção avançada do som (M = 71,35; DP = 20,22), limitação às atividades (M = 69,75; DP = 21,26) e interações sociais (M = 68,50; DP = 18,06) posicionaram-se acima da média e os domínios perceção básica do som (M = 64,40; DP = 20,90), produção da fala (M = 57,91; DP = 22,10) e autoestima (M = 59,05; DP = 15,23) abaixo da média.

A reprodutibilidade do questionário foi testada utilizando o coeficiente de correlação interclasses (Tabela 4), pois os dados eram numéricos e seguiam uma distribuição normal. Os resultados mostraram uma forte concordância entre avaliadores. O coeficiente α de Cronbach foi utilizado para avaliar a consistência interna da escala. A Tabela 4 apresenta os resultados obtidos para o α de Cronbach, a correlação média inter-item e a amplitude da correlação item-total. O total do questionário e todos os subdomínios apresentaram valores de consistência interna adequados, com valores α de Cronbach entre 0,82 (autoestima) e 0,96 (total da escala).

Tabela 2 – Características dos utilizadores de IC

Características	n = 50
Idade (anos)	55,50 ± 15,69
Género masculino (nº e %)	22 (44%)
Tempo de uso do implante (meses)	58,62 ± 48,56
Uso de implante por dia (nº e %)	
0 - 8 h	1 (2%)
9 - 12 h	15 (30%)
13 - 16h	20 (40%)
Desconhecido	14 (28%)
Causas de surdez (nº e %)	
Hereditária	9 (18%)
Otite média crónica	3 (6%)
Otosclerose	2 (4%)
Autoimune	2 (4%)
Meningite	1 (2%)
Desconhecida	33 (66%)

DISCUSSÃO

O objetivo deste estudo foi traduzir, adaptar culturalmente e validar para o Português Europeu o *Nijmegen Cochlear Implantation Questionnaire* (NCIQ). A validação desta escala vem disponibilizar à comunidade clínica portuguesa uma ferramenta útil para avaliar a qualidade de vida em adultos utilizadores de IC. Sendo o serviço de Otorrinolaringologia do Centro Hospitalar de Lisboa Ocidental um centro de referência nacional na área dos implantes cocleares aprovado pelo Ministério da Saúde, foi sentida a necessidade de se dispor de uma ferramenta como esta, que

Tabela 3 – Análise descritiva dos resultados nos domínios e subdomínios do questionário (n = 50)

Domínio	Subdomínio	M	DP	min	máx
Físico		64,82	18,11	19,17	97,5
	Perceção básica do som	64,40	20,90	20	97,5
	Perceção avançada do som	71,35	20,22	17,5	100
	Produção da fala	57,91	22,10	10	97,5
Psicológico					
	Autoestima	59,05	15,23	20	87,5
Social		69,13	18,82	21,25	95,0
	Limitação às atividades	69,75	21,26	12,5	97,5
	Interações sociais	68,50	18,06	20	100
Global		65,07	16,21	18,33	95,42

M: média; DP: desvio-padrão; min: mínimo; máx: máximo

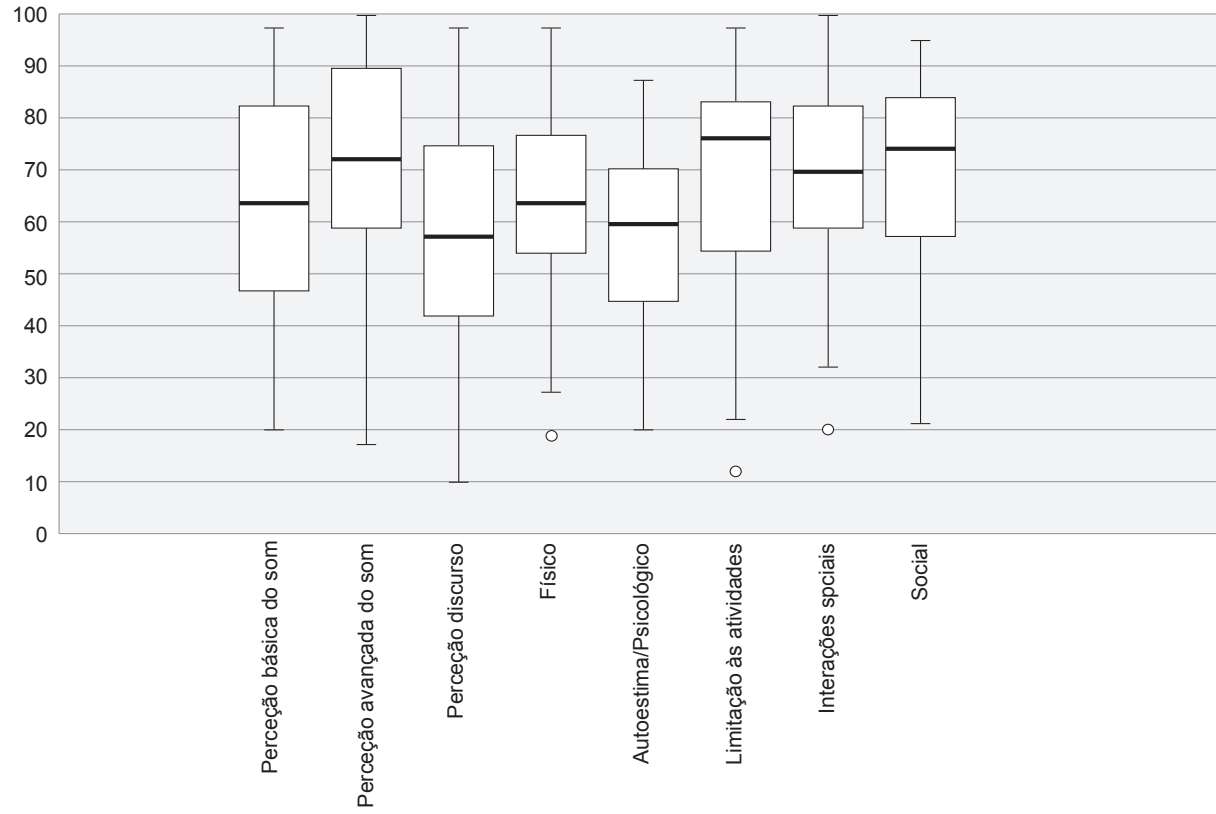

Figura 1 – Pontuações obtidas para os domínios e subdomínios do NCIQ para Português Europeu

permitirá avaliar a satisfação dos seus doentes de forma multidimensional, identificar áreas problemáticas e melhorar o seguimento clínico dos doentes.

O *Nijmegen Cochlear Implant Questionnaire* é utilizado clinicamente para avaliar a qualidade de vida após o implante coclear.[26,27] Já existe uma ampla utilização desta escala no cenário clínico internacional, estando disponíveis traduções e validações da escala em diversas línguas, entre as quais o espanhol, italiano e mandarim.[28-30]

A nossa versão do NCIQ para o Português Europeu (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16632/Apendice_01.pdf) apresentou uma forte consistência interna (valor do coeficiente de α de Cronbach de 0,96), em linha, e até superior, às descritas na literatura.[11,28-30] O NCIQ fornece uma pontuação global e uma pontuação para cada um dos seus três domínios e seis subdomínios (Fig. 2). Os resultados obtidos neste estudo demonstraram um nível de satisfação global de 65,07 nos utilizadores de IC. O domínio social foi o que apresentou maior pontuação, traduzindo uma melhoria nas capacidades auditivas e da interação social dos utilizadores de IC.[31,32] A elevada pontuação do subdomínio perceção avançada do som reflete a melhoria na compreensão da fala e, consequentemente, na comunicação. Aliás, este subdomínio, conjuntamente com o subdomínio perceção básica do som, são os que melhor refletem o benefício dos utilizadores de IC no acesso aos sons e à fala.[15,26,27,31,33] Em relação ao trabalho original de Hinderink, os valores dos subdomínios são similares exceto na perceção avançada do som e na produção da fala. Todos os sujeitos

Tabela 4 – Avaliação global e nos seis subdomínios para a consistência interna (α de Cronbach) e reprodutibilidade teste-reteste (coeficiente de correlação intraclasse) do NCIQ

Subdomínio	α de Cronbach	Correlação média inter-item	Amplitude da correlação item-total	Correlação interclasses
Perceção básica do som	0,88	0,42	0,309 - 0,726	0,97
Perceção avançada do som	0,87	0,41	0,369 - 0,759	0,98
Produção da fala	0,88	0,42	0,344 - 0,749	0,97
Autoestima	0,82	0,31	0,286 - 0,700	0,94
Limitação às atividades	0,88	0,43	0,332 - 0,782	0,96
Interações sociais	0,83	0,34	0,039 - 0,760	0,95
Total	0,96	0,27	0,042 - 0,757	0,99

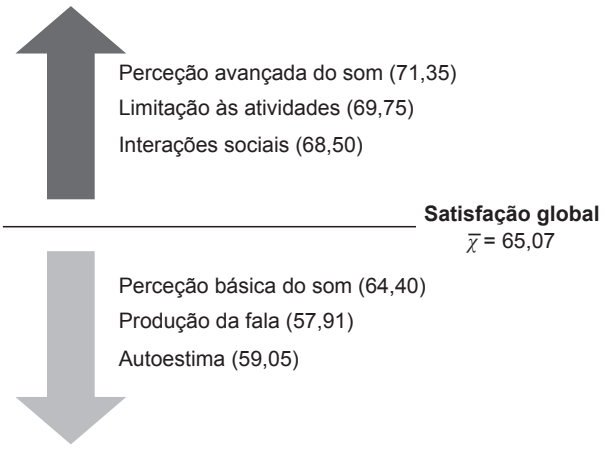

Figura 2 – Posicionamento dos subdomínios em relação à satisfação global da escala

completaram totalmente os questionários, sugerindo que entenderam todas as perguntas e ficaram à vontade para responder a todas elas. A consistência interna foi boa, com valores do coeficiente α de Cronbach superiores a 0,80 em todos os seis subdomínios do questionário. Foram mantidos todos os itens da escala já que nenhum item mostrou desvirtuar a consistência interna do domínio a que pertencia ou do total da escala. Deste modo, retirar itens iria alterar a validade de constructo da medida e não contribuiria para melhorar de forma significativa a consistência interna que já é adequada.

No nosso estudo, a adaptação cultural e a avaliação da reprodutibilidade da escala foram realizadas numa amostra de 21 indivíduos do grupo em estudo, de acordo com o número sugerido na literatura (20 a 40 indivíduos).[24,34] Para a sua validação utilizámos uma dimensão de amostra (n = 50) que permitisse o estudo da consistência interna e que, apesar não ser elevada, é até superior à do estudo original (n = 45).[11] Apesar dos bons resultados obtidos, é importante referir que a satisfação sentida com o IC pode variar em função de diversos fatores tais como a causa da surdez, o tempo de privação sensorial, a idade do diagnóstico e da intervenção, a diferenciação escolar, a motivação e o apoio familiar.[27,31,35] Adicionalmente, a subjetividade associada ao termo 'qualidade de vida' também deve ser considerada, uma vez que se relaciona com a perceção individual que cada indivíduo tem em relação à sua situação de saúde.

Existem diversos questionários para avaliar a qualidade de vida nos pacientes utilizadores de IC, mas são habitualmente demorados, difíceis de preencher e com reduzida sensibilidade a pequenas melhorias ou deterioração.[18] O *Glasgow Benefit Inventory* (GBI) é um questionário que, não sendo específico, pode ser adaptado para pacientes submetidos a implante coclear e[36] avalia alterações na qualidade de vida em relação a uma situação anterior inespecífica, sem referência, por exemplo, ao período de pré-implantação. O *Satisfaction with Amplification in Daily Life* (SADL) utiliza um questionário simples e de fácil aplicação para avaliar a adaptação às próteses auditivas, podendo também ser adaptado ao IC, e já foi também traduzido e validado para o português europeu pelos autores deste trabalho.[37,38] O questionário *Abbreviated Profile of Hearing Aid Benefit* (APHAB) quantifica os problemas vivenciados na comunicação em situações da vida diária, sendo composto por 24 questões de múltipla escolha, formuladas positiva ou negativamente. O APHAB tem como aspetos negativos a forma como as perguntas são elaboradas (algumas referem-se a situações com as quais os pacientes podem não estar familiarizados [teatro, conferências, serviços religiosos]), a complexidade do sistema de pontuação e a impossibilidade de pontuar se o questionário não for totalmente preenchido.[39] Por fim, não esclarece o impacto da perda auditiva na qualidade de vida do sujeito.

Uma das limitações do presente estudo podia ser o tamanho da amostra, embora consideremos que esta é adequada à população portuguesa. Outra limitação foi a ausência de comparação entre os dados obtidos e os resultados de testes de perceção da fala, o que poderia contribuir de forma significativa para a compreensão mais detalhada do impacto e efetividade desta escala. A extensão do questionário (60 questões) pode também ser considerada outra limitação à sua implementação plena na prática clínica. O trabalho original descreveu alguma falta de confiabilidade nos subdomínios da autoestima e produção da fala,[11] mas esse aspeto negativo não foi confirmado no nosso estudo. Por fim, um aspeto positivo do presente estudo é o momento da recolha das pontuações do NCIQ, que não foi realizada retrospetivamente.

CONCLUSÃO

A validação da escala NCIQ para o Português Europeu apresenta uma forte consistência interna, reprodutibilidade e sobreposição com os resultados positivos obtidos em outros estudos. Esta adaptação é um bom instrumento para a avaliação da satisfação dos utilizadores de implantes cocleares em Portugal dado que é a única escala que, para além de traduzida, está adaptada culturalmente para Português Europeu e validada para esse efeito. O facto de ser um questionário simples, com pontuação prática e índices numéricos, permite não só o seu uso clínico para uma avaliação multidimensional da satisfação nos utilizadores de implantes cocleares, mas também a comparação entre estudos e a investigação.

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CONTRIBUTO DOS AUTORES

LRR: Desenvolvimento e planeamento do projeto, recolha de dados, redação do manuscrito, processamento estatístico, revisão do manuscrito final.

LC, KG, FC, GN: Planeamento do projeto, recolha de dados, redação do manuscrito inicial.

RS, AO: Recolha de dados, redação do manuscrito inicial.

PE: Planeamento do projeto, redação do manuscrito inicial, revisão do manuscrito final.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Prophylaxis of Infective Endocarditis: A Cross Sectional Survey among Physician Members of the Portuguese Society of Cardiology

Estudo Transversal sobre Profilaxia da Endocardite Infecciosa: Inquérito a Médicos da Sociedade Portuguesa de Cardiologia

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ABSTRACT

Introduction: In the last decade, the downgrading of indications for antibiotic prophylaxis for infective endocarditis caused an uncertain impact on the incidence of this condition. Since no data is available on the practice of infective endocarditis prophylaxis in Portugal, we aimed to characterize the pattern of antibiotic use for infective endocarditis prophylaxis and the compliance/awareness of scientific guidelines among physician members of the Portuguese Society of Cardiology.

Material and Methods: A cross sectional observational study was conducted. An online self-completed questionnaire with 12 items on infective endocarditis prophylaxis was sent to 1330 physicians, specialists and residents, members of the Portuguese Society of Cardiology. In addition, descriptive statistical analysis was performed.

Results: Two hundred and fifty-three valid questionnaires were responded. Eighty-seven per cent of respondents were cardiologists (specialists or residents), mostly between 30 and 40 years old (26.7%) and 50 to 80 years old (44.3%). The majority (83.0%) follow the European scientific guidelines. Still, 61.0% had or may have had doubts regarding prophylaxis of infective endocarditis in certain patients. Variable adherence to scientific guidelines was noted. Further scientific evidence was required by 60.6% of respondents.

Conclusion: Infective endocarditis prophylaxis was generally guided by European scientific guidelines among physicians of the Portuguese Society of Cardiology. There was, however, an evident discrepancy between the guidelines and real-world perception of the risk of infective endocarditis. This highlights the sensed gap in accessing more robust scientific evidence.

Keywords: Antibiotic Prophylaxis; Endocarditis; Portugal; Surveys and Questionnaires

RESUMO

Introdução: Na última década, a restrição das indicações para a profilaxia antibiótica na endocardite infeciosa teve um impacto incerto na incidência desta condição. Uma vez que não existem dados sobre a prática da profilaxia da endocardite infeciosa em Portugal, procurámos caracterizar o padrão de utilização antibiótica para a profilaxia da endocardite infeciosa e a conformidade/sensibilização das orientações científicas entre médicos, membros da Sociedade Portuguesa de Cardiologia.

Material e Métodos: Foi realizado um estudo observacional transversal. Um questionário online de autopreenchimento com 12 itens sobre profilaxia da endocardite infeciosa foi enviado a 1330 médicos, especialistas e internos, sócios da Sociedade Portuguesa de Cardiologia. Foi realizada uma análise estatística descritiva.

Resultados: Foram validados 253 questionários respondidos. Oitenta e sete por cento dos inquiridos eram cardiologistas (especialistas ou internos), a maioria entre os 30 e os 40 anos (26,7%) e os 50 e 80 anos (44,3%). A maior parte (83,0%) segue as orientações científicas europeias. Ainda assim, 61,0% admitiu ter ou poder ter dúvidas sobre a profilaxia da endocardite infeciosa em determinados doentes. Verificou-se uma adesão variável às orientações científicas. A necessidade de mais evidência científica foi defendida por 60,6% dos respondedores.

Conclusão: Entre médicos da Sociedade Portuguesa de Cardiologia, a profilaxia da endocardite infeciosa foi geralmente orientada pelas orientações científicas europeias. Existiu, no entanto, uma evidente discrepância entre as orientações e a perceção do risco de endocardite infeciosa na prática clínica. Isto reforça a necessidade de acesso a dados científicos mais robustos.

Palavras-chave: Endocardite; Inquéritos e Questionários; Portugal; Profilaxia Antibiótica

INTRODUCTION

Despite tremendous medical advances, the management of infective endocarditis (IE) is clinically challenging and carries a substantial rate of morbidity and mortality worldwide.[1] Its crude incidence ranges from 1.5 to 11.6 cases per 100 000 people.[2] Moreover, in-hospital mortality rate affects nearly one-fifth of patients as documented in international registries such as the International Collaboration Endocarditis Cohort[3] or the recently published EURO-endo[4] (18% and 17%, respectively).

Approximately a century ago, the role of bacteremia leading to IE in patients with preexistent valve disease was demonstrated.[5] In addition, SD Elliot[6] demonstrated that transient bacteremia occurring following a dental infection or trauma could lead to subacute IE. Moreover, the concept of prevention through oral treatment emerged. In 1970, Hilson[7] defended the use of chemoprophylaxis for patients with increased susceptibility to endocarditis, citing Kelson and White who, in 1945, estimated a risk of endocarditis of

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1 in 500 after dental extraction.

Since then, several regimens have been proposed for the prevention of IE in susceptible patients. Scientific guidelines[8] include previous history of IE, prosthetic or repaired cardiac valves, cyanotic congenital heart disease and any repaired congenital heart disease for up to six months after repair or lifelong prophylaxis in residual shunt or regurgitation as high-risk cardiac conditions. The downgrading of antibiotic indications for endocarditis prevention in 2007 in the USA[9] and in 2009 in Europe[8] has, nonetheless, led to heterogeneous compliance by physicians, as shown by Chambers *et al*.[10] And this downgrading has not been adopted by several scientific societies, such as in Brazil or in Latin America. These still consider that native valve disease (such as aortic bicuspid valve or mitral valve prolapse) is a high risk situation and maintain antibiotic use before genitourinary or gastrointestinal procedures involving mucosa in high risk patients.[11]

Several electronic surveys conducted in Spain[12] or France[13] with dentists revealed that their knowledge of cardiac conditions and antibiotic side effects was inadequate.

The impact of this downgrading in antibiotic prophylaxis on the incidence of IE is still inconsistent[14] even though it has been shown in Germany[15] or in England.[16] In Portugal, no study has analyzed this impact on local or national incidence.[17,18] Nevertheless, an increasing trend was noted in the incidence of IE in Portugal in the last decade and the in hospital all-cause mortality rate affects one fifth of patients hospitalized with infective endocarditis.[17] The compliance of physicians with guidelines needs to be considered for quality and standard of care and assessment. No study has evaluated the pattern of antibiotic prophylaxis for IE among Portuguese physicians. Surveys are an essential tool to gather information on the attitudes and practice of care delivery among physicians.[19]

Therefore, we aimed to assess acceptance and compliance with scientific guidelines regarding IE prophylaxis among physician members of the Portuguese Society of Cardiology.

MATERIAL AND METHODS

Study design

A cross sectional descriptive study was carried out between the 8th February and the 28th February 2021, in a partnership between the Valvular Heart Diseases Working Group (Portuguese Society of Cardiology) and the Faculty of Medicine of the University of Lisbon.

After reviewing the most recent scientific guidelines[8,20] regarding antibiotic use in IE prevention, a 12 item questionnaire in Portuguese was developed (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17379/Appendix_01.pdf). All 12 questions were closed questions with an area in the end of the questionnaire for personal comments.

The questions regarding antibiotic prophylaxis in IE included data on 1) personal/professional background (age, specialty, year of medical degree), 2) international scientific guidelines and national/institutional guideline recommendations, 3) identification of high-risk conditions, 4) identification of high-risk procedures and 5) risk assessment and choice of antibiotics during dental procedures.

The questionnaire was planned to take less than five minutes to answer. All answers were anonymous. We gathered all quantitative and qualitative data for analysis. The questionnaire was active for three weeks and a reminder email was sent one week before the final date.

Sample

All physician members of the Portuguese Society of Cardiology (a total of 1330) were invited to participate in this online questionnaire, sent via email.

Statistical analysis

We performed a standard descriptive analysis of the results obtained from a convenience sample.

Continuous variables were presented as mean ± standard deviation and categorical variables were expressed as frequencies and percentages. Missing values were excluded from analyses (we performed an available data analysis).

The data were analyzed using Excel 365 for Windows software.

Table 1 – Characteristics of physicians that participated in the questionnaire

Medical Specialty		
Cardiology	190	74.5%
Resident - Cardiology	30	11.8%
Internal Medicine	4	1.6%
Resident - Internal Medicine	0	0.00%
Cardiothoracic surgery	9	3.5%
Resident - Cardiothoracic Surgery	1	0.4%
Paediatric Cardiology	16	6.3%
Family physician	1	0.4%
Not mentioned	4	1.6%
Age (year-old)		
20 to 30	26	10.2%
30 to 40	68	26.7%
40 to 50	41	16.1%
50 to 80	113	44.3%
> 80	5	2.0%
Year of Medical graduation		
1960 - 1989	99	39.3%
1990 - 1999	31	12.3%
2000 - 2009	61	24.2%
2010 - 2019	61	24.2%
Frequent evaluation of valve disease patients		
Yes	238	93.3%
No	16	6.3%

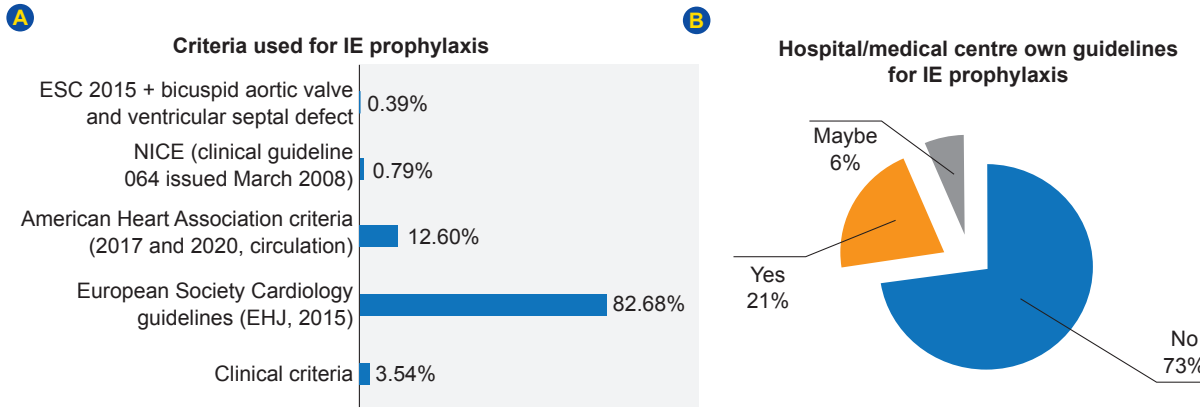

Figure 1 – (A) Usual criteria used by physicians for IE prophylaxis; (B) Institutional guidelines issued by medical institutions for antibiotic use in IE prevention.

Ethics

The Ethics Committee of the University of Lisbon Academic Centre study approved the study (reference number 349/19). All respondents gave their informed consent.

RESULTS

Of the 1330 invitations to physicians to participate in this survey, 255 questionnaires were returned, corresponding to a 19% response rate. However, two questionnaires contained no answers and were excluded. Most physicians were cardiologists and 60% of the participants were between 40 and 80 years old (Table 1); 93.3% reported regularly following patients with heart valve disease.

Compliance with scientific guidelines in IE prophylaxis

Nearly 83% of the respondents regularly followed the European Society of Cardiology scientific guidelines for IE prophylaxis (Fig. 1A). One quarter of physicians had institutional guidelines for IE prophylaxis (Fig. 1B).

Thirty nine percent of the respondents had no doubts regarding IE prevention (Fig. 2).

Cardiac conditions and procedures considered for IE prophylaxis

Patients with cardiac valve prosthesis, prosthetic material used in valvuloplasty, cyanotic congenital cardiac disease and previous IE were among the most frequently conditions identified by responders as high-risk conditions for IE (Table 2). The previous history of rheumatic valve disease was identified in 29.4% of the answers.

Most physicians identified dental procedures as a condition that increased the risk of IE, followed by implantation of intracardiac devices. Permanent tattooing and body piercing raised more doubts than any other procedure regarding the recommendation for IE prophylaxis (Fig. 3).

Dental procedures and IE

From the total number of respondents, 60.6% defended that further scientific evidence was needed to demonstrate the benefit of antibiotic use in invasive dental procedures.

Dental invasive procedures were identified as being high risk for the risk of IE whereas brushing teeth or eating was perceived as low risk activities (Fig. 4A). Nearly 93% of physicians used amoxicillin for IE prevention during dental procedures (Fig. 4B).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the current practice among physicians regarding IE prophylaxis in Portugal. In our study, applied to physicians who were members of the Portuguese Society of Cardiology, the European guidelines[8] were the most followed and the identification of high-risk cardiac conditions and procedures was mostly in accordance with them. Nonetheless, previous rheumatic fever, the presence of native valve disease or intracardiac devices were substantially identified as being high-risk cardiac conditions for IE, thus conflicting with current indications. Also, 61% of responders had doubts regarding IE prophylaxis in certain patients. Lastly, further evidence regarding dental procedures and IE prophylaxis was warranted by a substantial proportion of physicians.

The accepted standard of care relies more and more often on scientific expert guidelines. Ethically, though, deviation from these recommendations may be feasible if they are fully discussed with patients to ensure informed consent[21] and supported on scientific evidence.

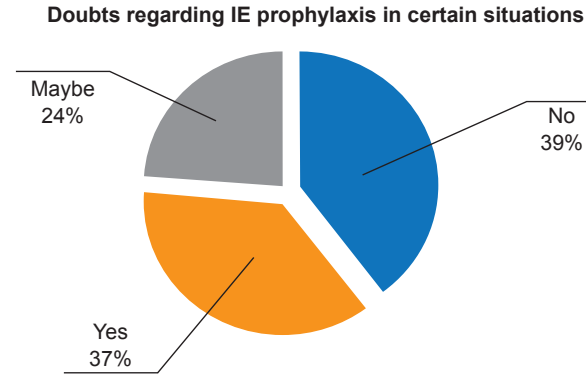

Figure 2 – Doubts regarding IE prophylaxis in clinical practice

Table 2 – Clinical conditions in which IE prophylaxis should be applied

Patients with cardiac valve prosthesis	241	94.5%
Patients with prosthetic material used in cardiac valvuloplasty	174	68.2%
Patients with history of rheumatic fever	75	29.4%
Patients with cyanotic congenital cardiac disease	228	89.4%
Patients with cardiac murmur or other evidence of native valve disease	32	12.6%
Patients with intracoronary stent intracoronary or coronary-aortic bypass graft surgery	6	2.4%
Patients with previous IE	230	90.2%
Patients with intracardiac device (pacemaker/implantable cardioverter defibrillator)	46	18.0%
All the options	6	2.4%
None of the options	4	1.6%
Other:		
Bicuspid aortic valve	3	1.2%
Recently implanted cardiac devices	1	0.4%
Patients with residual lesions after congenital defect repair	2	0.8%
Ventricular septal defect	1	0.4%
Percutaneous or surgically repaired congenital cardiac condition within 6 months of procedure	1	0.4%

From 2007 to 2009, several scientific societies[9,22,23] limited the use of antibiotic indication in the prophylaxis of IE. The United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) guidelines[22] were the most restrictive, advising against all forms of antibiotic use for IE prophylaxis. These overall measures were justified by the lack of scientific evidence of the benefit associated with the risk of inefficient use of antibiotics concerning side effects and increased risk of resistance.[8] Nevertheless, its impact has been controversial. A significant increase in the incidence of IE in England was noted by Dayer *et al*,[24] followed by similar findings in the Netherlands[25] and Germany.[25] Still, uncertainty persists[26] as significant heterogeneity between different studies and the follow-up period is still too short to allow drawing more permanent conclusions. Additionally, compliance can be challenging. Dayer *et al*[10] concluded that 39% of cardiologists/cardiac surgeons did not adopt the most recent NICE guidelines.

Most physician members of the Portuguese Society of Cardiology accepted the 2015 European guidelines.[8] Still, substantial conflict persists as many respondents expand IE prophylaxis use in cardiac conditions no longer

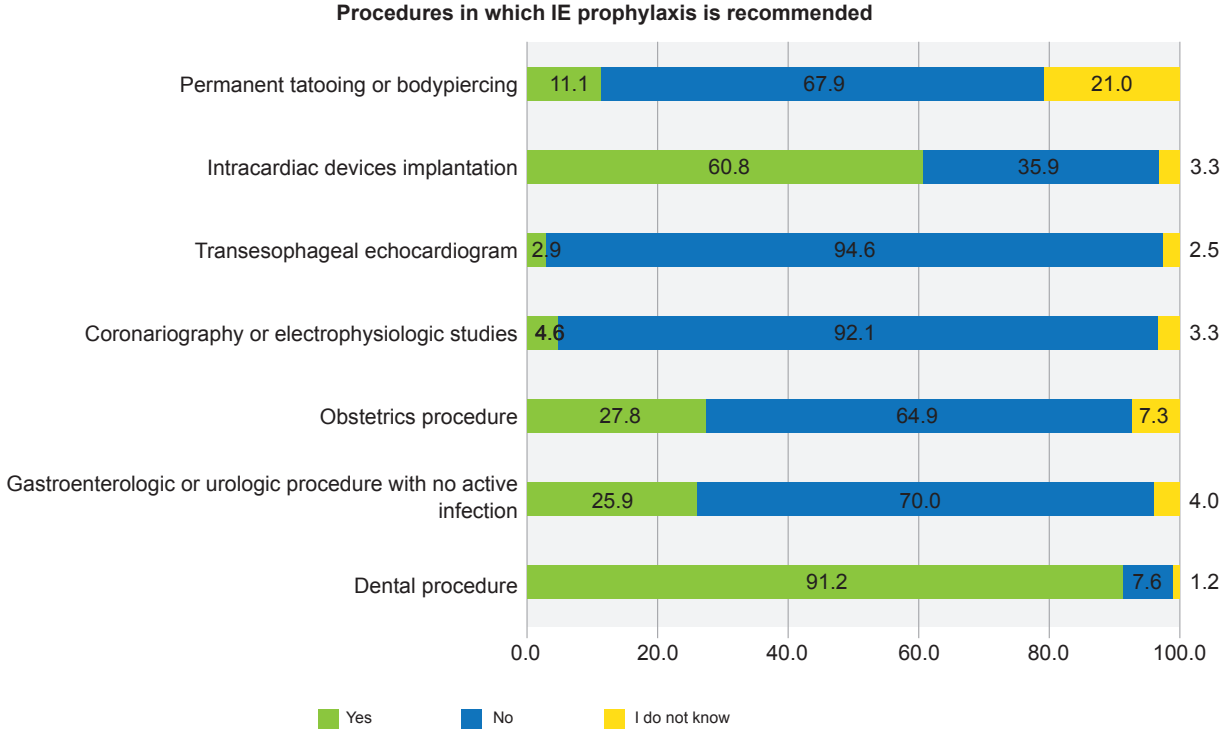

Figure 3 – IE prophylaxis recommendation in specific settings (%)

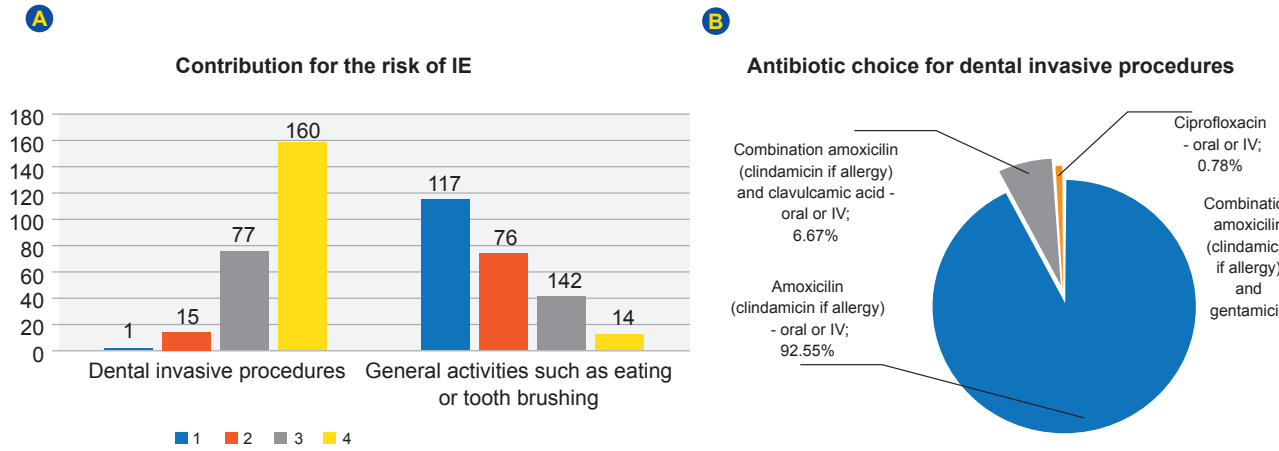

Figure 4 – (A) Perceived contribution that each of the following factors plays in the risk of developing infectious endocarditis (value of 1 to 4, being 1- no contribution and 4 - major contribution); (B) Antibiotic regimen (%) usually used in antibiotic prophylaxis in dental procedure.

considered high risk by the more recent guidelines, such as previous rheumatic fever, intracardiac devices or native valve disease carriers. Other studies have shown this heterogeneity. Grattan *et al*[27] concluded that among pediatric cardiologists, the 2007 American Heart Association guidelines[9] led to a reduction of IE prophylaxis recommendations among low risk patients by 44.9% but unexpectedly a reduction of 9.3% among high risk patients as well. This was also shown by Pharis *et al*[28] in a study carried out among New Zealand, Canada, Australia and American pediatric and adult congenital cardiologists in 2008.

The same is true for high-risk procedures. Dental procedures were almost always considered a high-risk situation by this group of 253 physicians. Nevertheless, other procedures currently removed from scientific guidelines such as obstetric procedures, urologic and gastroenterological procedures in the absence of active infection were also identified as procedures where IE prophylaxis was recommended. Remarkably, body piercing and permanent tattooing were the procedures that raised a significant proportion of doubt among respondents. In 2008, Armstrong *et al*[29] collated all cases of IE related to body art and concluded that transient bacteraemia can arise. Despite the fact that no antibiotic use is currently recommended by European guidelines,[8] education is crucial and in patients with high risk cardiac conditions and native valve disease these procedure should be discouraged.

Still, the epidemiology of infective endocarditis is changing worldwide.[4] Portugal is no exception. Patients hospitalized with IE in the last decade are older, have a higher burden of comorbidities such as arterial hypertension or diabetes *mellitus*, or cancer. There is an increasing proportion of patients with cardiac implantable electronic devices (CIED) or cardiac valve prosthesis.[17] Non-rheumatic valve disease is proportionally two-fold more frequent compared to rheumatic valve disease. Thornhill *et al*[30] also evaluated the impact of previous cardiac conditions on the risk of developing IE. Ultimately, in addition to the already known 'high risk' situations, other 'moderate risk' conditions such as congenital valve anomaly, hypertrophic cardiomyopathy, heart transplant, or left ventricle assist devices had a similar risk as some 'high risk' conditions. Contemporary risk stratification algorithms need to be revisited,[30,31] allowing for a better definition of prevention strategies. This is probably why in our study and in Pharis *et al*[28] a significant proportion of physicians expressed doubts regarding antibiotic use in IE prophylaxis in certain patients, probably for fear of leaving some at risk by not prescribing.

Regarding dental procedures, most respondents in our study considered invasive dental procedures to represent a higher risk of IE when compared with typical daily activities such as eating or brushing teeth. In 1977, Everett *et al*[32] reviewed bacteraemia occurring after several medical procedures and classified them almost always as short lived. However, the rate of post dental extraction bacteraemia was considered high (60% - 90%), which is substantially higher than with brushing teeth or dental flossing. Lockhart *et al*'s[33] 2008 study and a more recent meta-analysis by Cahill *et al*[26] concluded on the significant incidence of transient bacteraemia after tooth brushing. Still, transient bacteraemia is probably not the suitable surrogate for IE as it is more likely that low levels of bacteraemia occurring in most daily activities and medical procedures are insufficient to cause IE.[34] More robust and high-quality research is required, according to nearly two thirds of our responders.

Limitations

Firstly, a 19% response rate is considered low, which could partially implicate the impact of the presented results on the overall population of physicians dealing with valvular or congenital patients in Portugal. In fact, according to Abdulaziz K *et al*, physician surveys are characterized by a low response rate which can increase the presence of a nonresponse bias.[19] Nevertheless, higher response rates do not seem to impact the nonresponse bias in physician surveys.[35] The input of other specialities would be valuable to ascertain, namely dentists, family physicians or gastroenterologists and should deserve further analysis. Secondly, no further characterization of the location of the leading clinical activity was requested due to the compelling

requirement to maintain anonymity. This variable may, however, influence individual practice. Still, our study was not aimed at identifying why physicians have different practice patterns.

CONCLUSION

This survey is an initial effort to understand the practice of IE prophylaxis in Portugal. In this sample, IE prophylaxis is mostly guided by international scientific guidelines, mainly European. Nonetheless, there is some discrepancy regarding identifying high-risk cardiac conditions and procedures among professionals. Therefore, a substantial rate of uncertainty is assumed by most when deciding for certain patients and more scientific evidence is warranted. Interventions to promote continuous physician education should be considered, promoting a practice based on the best available evidence. Further studies should be conducted among other specialties outside of the scope of the Portuguese Society of Cardiology to take the complete national picture of IE prophylaxis practice.

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AUTHOR CONTRIBUTIONS

CSS: Data analysis, draft and critical review of the manuscript.

AGA, FJP: Data analysis, critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Multisystem Inflammatory Syndrome in Children Associated with COVID-19 in a Tertiary Level Hospital in Portugal

Síndrome Inflamatória Multissistémica em Crianças Associada a COVID-19 num Hospital de Nível III em Portugal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a rare and severe manifestation of coronavirus disease 2019 (COVID-19). The aim of this study was to describe the characteristics of children with MIS-C admitted to a pediatric tertiary hospital in Portugal.

Material and Methods: Observational descriptive study of MIS-C patients admitted between April 2020 and April 2021. Demographic and clinical characteristics, diagnostic tests, and treatment data were collected. The diagnosis of MIS-C was based on the World Health Organization and Centers for Disease Control and Prevention criteria.

Results: We reported 45 children with MIS-C. The median age was seven years (IQR 4 - 10 years) and 60.0% were previously healthy. SARS-CoV-2 infection was confirmed in 77.8% by RT-PCR or antibody testing for SARS-CoV-2, and in 73.3%, an epidemiological link was confirmed. All the patients had a fever and organ system involvement: hematologic (100%), cardiovascular (97.8%), gastrointestinal (97.8%), mucocutaneous (86.7%), respiratory (26.7%), neurologic (15.6%), and renal (13.3%) system. Neurological ($p = 0.035$) and respiratory ($p = 0.035$) involvement were observed in patients with a more severe presentation. There was a significant difference of medians when comparing disease severity groups, namely in the values of hemoglobin ($p = 0.015$), lymphocytes ($p = 0.030$), D-dimer ($p = 0.019$), albumin ($p < 0.001$), NT-proBNP ($p = 0.005$), ferritin ($p = 0.048$), CRP ($p = 0.006$), procalcitonin ($p = 0.005$) and IL-6 ($p = 0.002$). From the total number of children, 93.3% received intravenous immunoglobulin, 91.1% methylprednisolone, and one patient (2.2%) received anakinra. Thirteen patients (28.8%) required intensive care and there were no deaths. Of the 21 patients evaluated, 90.4% had reduction of exercise capacity and of the 15 patients who underwent cardiac magnetic resonance, 53.3% had sequelae of cardiac injury.

Conclusion: We observed a large spectrum of disease presentation in a group of patients where most were previously healthy. A small percentage of patients (28.9%) had a severe presentation of the disease. MIS-C is a challenge in current clinical practice and its diagnosis requires a high level of clinical suspicion as the timely initiation of therapy is essential to prevent complications. However, there is no scientific consensus on the treatment and follow-up of these patients.

Keywords: Child; COVID-19/complications; SARS-CoV-2; Systemic Inflammatory Response Syndrome

RESUMO

Introdução: A síndrome inflamatória multissistémica em crianças (MIS-C) é uma manifestação rara, mas grave da doença por coronavírus 2019 (COVID-19). Este estudo teve como objetivo descrever as características de crianças com MIS-C internadas num hospital pediátrico terciário em Portugal.

Material e Métodos: Estudo observacional e descritivo de doentes com MIS-C internados de abril de 2020 a abril de 2021. Analisaram-se dados demográficos, clínicos, exames de diagnóstico e terapêutica. O diagnóstico baseou-se nos critérios da Organização Mundial de Saúde e Centers for Disease Control and Prevention.

Resultados: Foram identificadas 45 crianças, com mediana de idades de sete anos (AIQ 4 - 10 anos) sendo 60,0% previamente saudáveis. A infeção por SARS-CoV-2 foi confirmada por RT-PCR ou serologia em 77,8% dos doentes e 73,3% tinham *link* epidemiológico. Todos os casos cursaram com febre e envolvimento multiorgânico: hematológico (100%), cardiovascular (97,8%), gastrointestinal (97,8%), mucocutâneo (86,7%), respiratório (26,7%), neurológico (15,6%) e renal (13,3%). O envolvimento neurológico ($p = 0,035$) e respiratório ($p = 0,035$) ocorreu nos doentes mais graves. Houve uma diferença significativa das medianas quando comparados grupos de gravidade da doença, nomeadamente nos valores de hemoglobina ($p = 0,015$), linfócitos ($p = 0,030$), D-dímeros ($p = 0,019$), albumina ($p < 0,001$), NT-proBNP ($p = 0,005$), ferritina ($p = 0,048$), pCr ($p = 0,006$), procalcitonina ($p = 0,005$) e IL-6 ($p = 0,002$). Destas crianças, 93,3% realizaram imunoglobulina intravenosa, 91% metilprednisolona e um (2,2%) realizou anakinra. Treze doentes (28,8%) necessitaram de cuidados intensivos e não se registaram óbitos. Dos 21 doentes avaliados seis meses após a alta, 90,4% apresentaram diminuição da tolerância ao esforço e 8/15 (53,3%) lesão cardíaca persistente.

Conclusão: Observámos um amplo espectro de apresentação da doença num grupo de doentes previamente saudável, na sua maioria. Uma pequena percentagem de pacientes (28,9%) teve uma apresentação grave da doença. O diagnóstico da MIS-C é um desafio na prática clínica atual e requer um elevado nível de suspeição pois o início atempado de terapêutica é fundamental para prevenir complicações. No entanto, não existe ainda consenso científico sobre a melhor terapêutica e seguimento destes doentes.

Palavras-chave: COVID-19/complications; Criança; SARS-CoV-2; Síndrome de Resposta Inflamatória Sistémica

INTRODUCTION

In December 2019, an outbreak of pneumonia emerged in the city of Wuhan, China.[1] The new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified on January 3rd, 2020 and

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was responsible for the coronavirus-disease 2019 (COVID-19).[1,2] A pandemic was declared on the 11th of March 2020.[1] The first case of COVID-19 in Portugal was confirmed on the 2nd of March, 2020, and the first pediatric case was confirmed on the 7th March, 2020.[3]

The COVID-19 pandemic has caused substantial morbidity and mortality worldwide, although the number of infected children and those with severe disease is significantly lower when compared to adults. However, in April 2020 in the United Kingdom, a cluster of healthy children with a previous SARS-CoV-2 infection presented with severe disease, hyperinflammatory shock, and features that overlapped with those of toxic shock syndrome and atypical Kawasaki disease (KD).[4,5] The Royal College of Paediatrics and Child Health referred to this condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).[6] This was followed by another report with features resembling not only KD but also secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome.[4,7,8] The United States Centers for Disease Control and Prevention (CDC), on the 14th May 2020, called this spectrum of COVID-19 in the pediatric population multisystem inflammatory syndrome in children (MIS-C) and introduced a case definition that was reproduced by the World Health Organization (WHO).[9,10]

On the 3rd May, 2021, a total of 3742 confirmed cases and 35 deaths due to MIS-C were reported in the United States of America.[11] Some estimates indicate that MIS-C occurs in two out of 100 000 individuals under 21 years old,[12] but the incidence is unknown, and it appears to be a rare complication of SARS-CoV-2 infection.[12]

MIS-C is characterized, according to the WHO and CDC criteria, by fever, multisystem involvement, and elevated inflammatory markers (Table 1), and it also includes evidence of a SARS-CoV-2 infection and no other microbial cause or alternative plausible diagnosis.[9,10]

The pathogenesis of MIS-C, although not well understood, is thought to be a postinfectious immune-mediated phenomenon, as seen from a time interval of four to six weeks between the occurrence of a peak incidence of COVID-19 cases in communities and MIS-C cases.[7,13-15] A postinfectious phenomenon related with IgG antibody-mediated enhancement of disease is also supported by reports of a higher prevalence of positive tests for SARS-CoV-2 antibodies rather than for positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (rRT-PCR).[16] The prognosis of MIS-C is uncertain because long-term follow-up data are limited.[17] We aim to describe the characteristics of children with MIS-C admitted to a pediatric tertiary hospital in Portugal.

MATERIAL AND METHODS

A case series descriptive study of pediatric patients, under the age of 18 years old, admitted to a pediatric

Table 1 – Case definitions for multisystem inflammatory syndrome in children from the World Health Organization and Centers for Disease Control and Prevention[9,10]

	WHO - World Health Organization	CDC - Centers for Disease Control and Prevention
Age	0 - 19 years of age	< 21 years
Fever	Fever for ≥ 3 days	Fever > 38.0°C for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours
Multisystem involvement	At least 2 clinical signs of multisystem involvement: 1. Rash, bilateral non purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) 4. Evidence of coagulopathy (prolonged PT, elevated D-dimers) 5. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)	Clinically severe illness requiring hospitalization Multisystem involvement (2 or more organ system involved): 1. Cardiovascular (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrythmia) 2. Respiratory (e.g., pneumonia, ARDS, pulmonary embolism) 3. Renal (e.g., AKI, renal failure) 4. Neurologic (e.g., seizure, stroke, aseptic meningitis) 5. Hematologic (e.g., coagulopathy) 6. Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) 7. Dermatologic (e.g., erythroderma, mucositis, another rash)
Inflammation markers	Elevated markers of inflammation (e.g., elevated, CRP, ESR or procalcitonin)	Laboratory evidence of inflammation (including, but not limited to ≥ 1 of the following): elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, neutrophilia, lymphocytopenia, hypoalbuminemia
Exclusion of other diagnosis	No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndromes.	No alternative plausible diagnosis
Evidence of SARS-CoV-2 infection	Any of the following: positive SARS-CoV-2 RT-PCR, positive serology, antigen test, contact with an individual with COVID-19	Any of the following: Positive SARS-CoV-2 RT-PCR, positive serology, positive antigen test, COVID-19 exposure within the 4 weeks prior to the onset of symptoms

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; BNP: brain natriuretic peptide; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; LDH: lactic dehydrogenase; PCT: procalcitonin; PT: pro-thrombin time; RT-PCR: real time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

tertiary level hospital in Portugal from April 2020 to April 2021, with MIS-C. MIS-C diagnosis was based on the WHO and CDC criteria (Table 1). The demographic data, underlying medical conditions, clinical findings and evolution, laboratory results, imaging findings, treatment, complications, and sequelae were analyzed.

We defined MIS-C severity as mild (minimal organ lesion), moderate (moderate to severe organ lesion and need of oxygen support), and critical (severe organ lesion with organ dysfunction or need of inotropic support).

The statistical analysis was performed using the Statistical Package for Social Sciences version 26 (IBM Corp., Armonk, NY, USA) software package. Prior to the statistical analysis, variables were assessed in terms of their normality (visual assessment) and all the variables were found to be non-normally distributed. The Clopper-Pearson exact 95% confidence interval (CI) was calculated for the prevalence of MIS-C in hospitalized patients with a SARS-CoV-2 infection. Continuous variables were expressed as medians and interquartile ranges (IQR) or ranges, and categorical variables were expressed as counts and percentages. Kruskal Wallis and Dunn's multiple comparison tests were used to test for the differences in continuous variables across groups of categorical ones. Bonferroni-adjusted significance tests for pairwise comparisons were used. Fisher's exact test was used to study associations between categorical variables, after disregarding chi-square test due to more than 20% cells with expected count less than 5. A *p* value under 0.05 was considered statistically significant. Patients were not directly studied, and their informed consent was not deemed necessary because the data collected was retrospective and immediately anonymized. Analysis was based on retrospective data collection without any identification of patients thus not requiring specific ethics committee approval.

RESULTS

Of the 312 patients hospitalized with a SARS-CoV-2 infection, 45 had MIS-C (14.4%), which is a prevalence rate of MIS-C in hospitalized patients with SARS-CoV-2 infection of 14.4% (CI 10.7, 18.8). The first case was reported on the 23rd April 2020. The median age was seven years (IQR 4 - 10 years), 31 (68.9%) children were male, and eight (17.8%) were of African ancestry. Twenty-seven (60.0%) were previously healthy (defined as patients without chronic disease as collected from the medical history), and 18 (40.0%) had a chronic disease: obesity (9/45), asthma (4/45), kidney disease (2/45), congenital heart defect (1/45), long gap esophageal atresia (1/45), and epilepsy (1/45).

Twenty-four (53.3%) patients had a history of a previous SARS-CoV-2 infection, 30 (66.7%) reported contact with a sick household member and three (6.7%) with children in school with a confirmed SARS-CoV-2 infection by rRT-PCR. The median duration from contact with a patient with positive rRT-PCR SARS-CoV-2 to the patient's symptom onset was 33 days (range 16 - 60 days, IQR 27 – 44 days).

At the time of MIS-C diagnosis, 35 patients (77.8%) had laboratory evidence of a SARS-CoV-2 infection: 21 patients (46.6%) had positive SARS-CoV-2 antibodies, two patients (2.2%) had positive SARS-CoV-2 rRT-PCR, and 12 patients (26.7%) had both rRT-PCR and antibodies for SARS-CoV-2. Of the 10 patients (22.2%) without laboratory evidence of a SARS-CoV-2 infection, all of them reported an epidemiological context with COVID-19 exposure.

The most common symptoms at hospital admission were fever (45/45, 100%), followed by abdominal pain (27/45, 60%), vomiting (24/45, 53.3%), rash (22/45, 48.9%), and bilateral conjunctival hyperemia (13/45, 28.9%). The median duration from symptom onset to hospital admission was six days (range 2 - 15 days, IQR 4 - 8 days). The clinical

Table 2 – Clinical characteristics of patients according to SARS-CoV-2 rRT and SARS-CoV-2 antibodies

	Total of patients (n = 45)	**Positive SARS-CoV-2 rRT PCR** (n = 14)	**Positive SARS-CoV-2 antibodies** (n = 33)
Fever	45/45 (100%)	14/14 (100%)	33/33 (100%)
Hypotension	12/45 (26.7%)	4/14 (8.9%)	11/33 (33.3%)
Abdominal pain	37/45 (82.2%)	11/14 (78.6%)	29/33 (87.9%)
Vomiting	32/45 (71.1%)	10/14 (71.4%)	23/33 (69.7%)
Diarrhea	14/45 (31.1%)	6/14 (16.7%)	11/33 (33.3%)
Cutaneous rash	34/45 (75.6%)	10/14 (71.4%)	25/33 (75.8%)
Bilateral conjunctival hyperemia	28/45 (62.2%)	9/14 (64.3%)	21/33 (63.6%)
Enanthema	12/45 (26.7%)	4/14 (28.6%)	10/33 (30.3%)
Dyspnea	8/45 (17.8%)	2/14 (14.3%)	8/33 (24.2%)
Peripheral edema	6/45 (13.3%)	3/14 (21.4%)	4/33 (12.1%)
Cervical lymphadenopathies	5/45 (11.1%)	3/14 (21.4%)	3/33 (9.1%)
Headache	10/45 (22.2%)	3/14 (21.4%)	7/33 (21.2%)
Neck stiffness	3/45 (6.7%)	1/14 (7.1%)	2/33 (6.1%)
Gait imbalance	1/45 (2.2%)	1/14 (7.1%)	1/33 (3.0%)

rRT-PCR: real-time reverse-transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

characteristics of patients with positive SARS-CoV-2 rRT-PCR and positive SARS-CoV-2 antibodies are displayed in Table 2.

All patients had at least three organ systems involved. The most common were hematologic (45/45, 100%), cardiovascular (44/45, 97.8%), gastrointestinal (44/45, 97.8%), and mucocutaneous (39/45, 86.7%). Respiratory system involvement occurred in 12/45 (26.7%), nervous system involvement in 7/45 (15.6%), and renal system involvement in 6/45 (13.3%). Neurological involvement (p = 0.035) and respiratory involvement (p = 0.041) were associated with the severity of MIS-C (Table 3). Although renal involvement did not show a statistically significant association with severity, it is possible to state by analyzing the data presented in Table 3 that the percentage of patients with renal involvement increased with the severity of the disease.

Regarding hematologic manifestations, 33 patients (73.3%) had anemia, 21 (46.7%) had lymphocytopenia, 38 (84.4%) had elevated prothrombin time (PT), 29 (64.4%) had elevated fibrinogen, and 45 (100%) had elevated D-dimer. We observed elevated lactic dehydrogenase (LDH) in 30 (66.7%) patients and hypoalbuminemia in 33 (73.3%) patients (Table 4). The Kruskal Wallis test provided evidence of significant difference between median peak values in at least one pair of disease severity groups in hemoglobin (p = 0.015), lymphocytes (p = 0.030), D-dimer (p = 0.019) and albumin (p < 0.001). Regarding the median minimum value of hemoglobin there was a significant difference between moderate and critical MIS-C (p = 0.011), in minimum value of lymphocytes (p = 0.030) and maximum value of D-dimer (p = 0.026) significant differences between mild and critical MIS-C, in minimum value of albumin significant differences between mild and critical MIS-C (p = 0.011) and moderate and critical MIS-C (p = 0.002) (Table 5).

Forty-four patients (97.8%) had elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and 20 patients (44.4%) had elevated troponin I levels (Table 4). As for cardiovascular involvement, nine patients (20.0%) needed vasoactive support. There was a significant difference in the medians of maximum peak values of NT-proBNP between groups of disease severity (p = 0.005), with medians in both mild and critical MIS-C (p = 0.025) and moderate and critical MIS-C (p = 0.018) having significant differences (Table 5).

The ECG showed sinus bradycardia in two patients (4.4%) and a first-degree atrioventricular block in one patient (2.2%). Six patients (13.3%) had echocardiographic evidence of perivascular echogenicity of coronary arteries and two patients (4.4%) had evidence of coronary artery aneurysms. We also observed mitral regurgitation (11/45, 24.4%), tricuspid regurgitation (3/45, 6.7%), left ventricular disfunction (4/45, 8.9%), pericardial effusion (5/45, 11.1%), and a patient who had a congenital heart defect had overlap abnormalities compared with the imaging test performed before the MIS-C diagnosis.

We observed ascites in 15 patients (33.3%), mesenteric adenitis in 11 (24.4%), inflammation of the appendix in five (11.1%), ileitis in three (6.7%), colitis in two (4.4%), hepatomegaly in seven (15.6%), splenomegaly in five (11.1%), and gallbladder wall thickening in three (6.7%). Three patients (6.7%) underwent an appendicectomy due to an early presentation with appendicitis.

Mucocutaneous manifestations were present in 39 children (86.7%) with a spectrum of manifestations including cutaneous rash, petechiae, bilateral conjunctival hyperemia, mucositis, cheilitis, and desquamation of the fingers and toes.

Eleven patients (24.4%) had pneumonia identified in a radiography, and 10 patients (22.2%) had evidence of pleural effusion. Respiratory failure occurred in nine patients (20.0%), with one patient needing invasive mechanical ventilation.

Neurological involvement was observed in seven patients (15.6%) and was characterized by headache (2/45,

Table 3 – MIS-C patient severity and patient's characterization

	Total of patients (n = 45)	**Mild MIS-C** (n = 3)	**Moderate MIS-C** (n = 29)	**Critical MIS-C** (n = 13)	***p*-value**
Male	31/45 (68.9%)	2/3 (66.7%)	20/29 (69.0%)	9/13 (69.2%)	1.000[a]
African ancestry	8/45 (17.8%)	0/3 (0%)	5/29 (17.2%)	3/13 (23.1%)	0.828[a]
Obesity	9/45 (20.0%)	0/3 (0%)	7/29 (24.1%)	2/13 (15.4%)	0.847[a]
Positive PCR SARS-CoV-2	14/45 (31.1%)	0/3 (0%)	10/29 (34.5%)	4/13 (30.8%)	0.669[a]
Positive SARS-CoV-2 antibodies	33/45 (73.3%)	3/3 (100%)	18/29 (62.1%)	12/13 (92.3%)	0.070[a]
25(OH)D insufficiency or deficiency	32/38 (84.2%)	1/3 (33%)	20/23 (87.0%)	11/12 (91.7%)	0.079[a]
Cardiovascular involvement	44/45 (97.8%)	2/3 (66.7%)	29/29 (100%)	13/13 (100%)	0.067[a]
Gastrointestinal involvement	44/45 (97.8%)	3/3 (100%)	29/29 (100%)	12/13 (92.3%)	0.356[a]
Hematological involvement	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)	Nd[a]
Mucocutaneous involvement	39/45 (86.7%)	1/3 (33%)	26/29 (89.7%)	12/13 (92.3%)	0.056[a]
Neurological involvement	7/45 (15.6%)	0/3 (0%)	2/29 (6.9%)	5/13 (38.5%)	0.035[a]
Renal involvement	6/45 (13.3%)	0/3 (0%)	2/29 (6.9%)	4/13 (30.8%)	0.091[a]
Respiratory involvement	12/45 (26.7%)	0/3 (0%)	5/29 (17.2%)	7/13 (53.8%)	0.041[a]

[a]: Fischer's exact test. 25(OH)D: serum 25-hydroxyvitamin D; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 4 – MIS-C patient severity and abnormal laboratory values

	Total of patients no, %	Mild MIS-C (n = 3)	Moderate MIS-C (n = 29)	Critical MIS-C (n = 13)
Hb < 11 g/dL	33/45 (73.3%)	3/3 (100%)	18/29 (62.1%)	12/13 (92.3%)
Lymphocytes < 1000 cells/µ	21/45 (46.7%)	0/3 (0%)	12/29 (41.4%)	9/13 (69.2%)
PT > 13 sec	38/45 (84.4%)	3/3 (100%)	26/29 (89.7%)	9/13 (69.3%)
Fibrinogen > 5.0 g/L	29/45 (64.4%)	0/3 (0%)	19/29 (65.5%)	9/13 (69.2%)
D-dimer > 230 µg/L	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)
LDH > 300 U/L	30/45 (66.7%)	2/3 (66.7%)	19/29 (65.6%)	9/13 (69.2%)
Albumin < 38 g/L	33/45 (73.3%)	0/3 (0%)	21/28 (75.0%)	12/13 (92.3%)
CRP > 5 mg/L	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)
Procalcitonin > 0.1 ng/mL	43/45 (95.6%)	2/3 (66.7%)	28/29 (96.6%)	13/13 (100%)
ESR > 11 mm/h	43/43 (100%)	3/3 (100%)	28/28 (100%)	12/12 (100%)
IL-6 > 4 pg/mL	42/43 (97.7%)	3/3 (100%)	26/27 (96.3%)	13/13 (100%)
Ferritin > 79 ng/mL	44/44 (100%)	3/3 (100%)	28/28 (100%)	13/13 (100%)
Amyloid A > 6.5 mg/L	32/33 (97.0%)	3/3 (100%)	19/19 (100%)	10/11 (90.0%)
Troponin I > 35 ng/mL	20/45 (44.4%)	1/3 (33%)	10/29 (34.5%)	9/13 (69.2%)
NT-pro-BNP (superior to higher limit depending with age group[a])	44/45 (97.8%)	3/3 (100%)	28/29 (96.6%)	13/13 (100%)

Laboratory values analyzed were peak values. Thresholds values were obtained from local laboratory reference ranges.
[a]: NT-pro-BNP normal range by age group < 1 month: 263 - 6500 ng/L, < 12 months: 37 - 1000 ng/L, 12 months - 35 months: 39 - 675 ng/L, 3-6 years: 23 - 327 ng/L, 7 - 14 years: 10 - 242 ng/L, 15 - 18 years: 6 - 207 ng/L[37]
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; IL-6: interleukin-6; LDH: lactic dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; PT: pro-thrombin time

4.4%), psychomotor agitation (1/45, 2.2%), meningism (1/45, 2.2%), and bilateral sixth nerve palsy (1/45, 2.2%). Two patients had aseptic meningitis (4.4%) with the cerebrospinal fluid analysis showing pleocytosis with mononuclear cells predominance and mild high cerebrospinal fluid (CSF) protein concentrations. One patient with bilateral sixth nerve palsy had a positive SARS-CoV-2 serology in their cerebrospinal fluid.

Four patients (8.9%) had acute kidney injury, one patient (2.2%) had proteinuria and hematuria, and one patient (2.2%) had orchiepididymitis with a testicular ultrasound presenting enlargement and hypervascularity of both epididymis and spermatic cord enlargement.

An adolescent with an initial diagnosis of a retropharyngeal phlegmon with a cervical adenophlegmon developed clinical (with left ventricular cardiac aneurysms) and laboratory findings that were consistent with MIS-C, an atypical presentation for MIS-C.

All the patients had four or more laboratory biomarkers of inflammation such as elevated C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), serum amyloid A, and ferritin (Table 4) with a tendency for normalization at the time of discharge. Regarding ferritin, although there was evidence of significant difference of median peak value between groups of disease severity ($p = 0.048$), there was no significant difference in a specific pair of groups. There was a significant difference in median maximum values of CRP ($p = 0.006$), procalcitonin ($p = 0.005$) and IL-6 ($p = 0.002$) between groups of disease severity. Significant difference comparing medians both in mild and critical MIS-C and moderate and critical MIS-C was found in CRP ($p = 0.040$, $p = 0.018$), procalcitonin ($p = 0.018$, $p = 0.026$) and IL-6 ($p = 0.004$, $p = 0.033$) (Table 5).

Three patients (6.7%) had minimal organ lesions, 29 patients (64.4%) had moderate to severe organ lesions and the need of oxygen support, and 13 (28.9%) had severe organ lesions with organ dysfunction or the need of inotropic support. Regarding the patients who had a severe phenotype of MIS-C, 13 (81.2%) required intensive care, seven (43.8%) were diagnosed with distributive shock, four (25%) with cardiogenic and distributive shock, nine (56.3%) needed vasoactive support, and one (6.3%) mechanical ventilation due to severe hypoxia. Kawasaki-like phenotype was observed in 18 patients (40.0%), and of those, 14 patients (31.1%) presented an incomplete Kawasaki-like phenotype.

In three patients with the mildest form of the syndrome, an expectant attitude was taken with good clinical evolution. Forty-two patients (93.3%) received intravenous immunoglobulin (2 g/kg single dose or 1 g/kg for two days if hemodynamic instability). Methylprednisolone therapy was administered to 41 patients (91.1%): 35 patients (77.8%) at 2 mg/kg/day and six patients (13.3%) at 10 - 30 mg/kg/day. Higher doses of methylprednisolone were used in patients with a severe presentation of MIS-C, as the therapeutic failure of first-line drugs occurred. Two patients treated with corticosteroids developed hypertension. One patient (2.2%) with severe MIS-C experienced the failure of the first line treatment, and for that reason, received anakinra as a second line therapy.

Forty-three patients (95%) received empirical broad spectrum antibiotics, most of them (33/45, 73.3%) with ceftriaxone and clindamycin. The other therapeutic agents

Table 5 – MIS-C patient severity and peak value during hospitalization

	Median values (interquartile range)				**Kruskal Wallis test**		**Dunn's multiple comparisons tests**		
	Total of patients	Mild MIS-C	Moderate MIS-C	Critical MIS-C	Test value	*p* value	Mild – Moderate MIS-C	Mild – Critical MIS-C	Moderate – Critical MIS-C
Hb g/dL*	10.40 (9.30 - 11.40)	10.4	10.8	9.2	8.426	0.015	1.000	0.700	0.011
Lymphocytes cells/µ*	1000.00 (620.00 - 1585.00)	2910	1000	800	6.996	0.030	0.173	0.030	0.408
PT sec[a]	15.00 (13.90 – 16.25)	14.1	15.6	14.1	3.820	0.148	N/a	N/a	N/a
Fibrinogen g/L*	5.40 (4.45 – 6.30)	4.7	5.5	5.8	2.041	0.360	N/a	N/a	N/a
D-dimer µg/L[a]	944.00 (572.00 – 1993.50)	531	920	1741	7.895	0.019	0.244	0.026	0.183
LDH U/L[a]	340.0 (293.50 – 407.50)	355	317	344	0.071	0.965	N/a	N/a	N/a
Albumin g/L*	29.90 (25.00 – 37.50)	40.4	33.1	25	15.413	< 0.001	0.445	0.011	0.002
CRP mg/L[a]	197.60 (142.10 – 292.75)	121.1	169.9	295.9	10.093	0.006	0.813	0.040	0.018
Procalcitonin ng/Ml[a]	1.54 (0.67 – 4.83)	0.42	1.35	3.78	10.640	0.005	0.434	0.018	0.026
ESR mm/h[a]	71.00 (59.00 – 81.00)	75	68.5	74	1.335	0.513	N/a	N/a	N/a
IL-6 pg/mL[a]	105.9 (45.20 – 415.00)	8.12	62	415	12.356	0.002	0.159	0.004	0.033
Ferritin ng/mL[a]	418.50 (262.15 – 889.68)	276.7	378.9	689	6.057	0.048	0.306	0.056	0.382
Amyloid A mg/L[a]	714.00 (409.00 – 1235.00)	246	714	940	0.796	0.672	N/a	N/a	N/a
Troponin I ng/mL[a]	28.00 (2.40 – 260.65)	38	12.1	149	5.057	0.080	N/a	N/a	N/a
NT-pro-BNP ng/L[a]	2970.00 (1518.50 – 7738.00)	354.5	2241	9576	10.672	0.005	0.600	0.025	0.018

*: peak value regarding the minimum value during hospitalization, [a]: peak value regarding the maximum value during hospitalization.
N/a: Dunn's multiple comparisons test is not performed as the entire test does not show significant differences between samples;
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; IL-6: interleukin-6; LDH: lactic dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; PT: pro-thrombin time.

included enoxaparin (prophylactic doses) in 17 patients (37.8%), acetylsalicylic acid in 22 patients (48.9%), and gastric protection in 42 (93.3%). Vitamin D supplementation was administered to 32 patients (71.1%): 18 (40%) with vitamin D deficiency and 14 (31.1%) with insufficiency.

Cytomegalovirus reactivation was observed in one patient. One patient presented macrophage activation syndrome, toxicoderma, and disseminated herpes simplex virus type 1 infection and received valacyclovir, two cycles of methylprednisolone therapy (one at 30 mg/kg/day and other at 10 mg/kg/day), and second line immunosuppression treatment with anakinra with a good outcome.

Significant weight loss (defined as at least 10% weight loss) associated with MIS-C was observed in five patients (11.1%), median weight loss 8.4% (IQR 5.95 - 14.55%).

Patients were discharged with a median length of stay of nine days (range 3 - 28 days, IQR 7.00 - 12.50 days) and there were no fatalities.

All the children underwent outpatient follow-up (minimum eight months - to date, all patients still have follow-up appointments) and performed multidisciplinary evaluations (infectious diseases, cardiology, physical and rehabilitation medicine, nutrition, and psychology). Thirty-two of the 44 patients (72.7%) with cardiac involvement underwent an echocardiogram two to eight weeks after discharge: 30 (30/32, 93.7%) had a normal echocardiogram and two (2/32, 6.3%) presented coronary artery abnormalities and these patients belonged to the group of patients with coronary abnormalities diagnosed during hospitalization. Fifteen of the 44 patients (15/44, 34.1%) underwent cardiac magnetic resonance imaging (MRI) because of systolic dysfunction or cardiac injury in the acute period and eight (8/15, 53.3%) presented myocardial fibrosis. Of those, four patients (4/15, 26.7%) presented subacute myocarditis, two (2/15 13.3%) subacute pericarditis, one (1/15, 6.7%) coronary artery ectasia, and one (1/15, 6.7%) left ventricle dilatation.

Seven patients with respiratory involvement (7/12, 58.3%) performed pulmonary function tests and one patient (1/7, 14.3%) revealed abnormal diffusion and another patient (1/7, 14.3%) showed abnormal resistance.

Five patients who had renal system involvement (5/6, 83.3%), performed a renal scintigraphy that showed renal scars in three (3/5, 60%) and a subacute lesion in one (1/5, 20%).

Twenty-one patients (21/45, 46.7%) were evaluated by physical and rehabilitation medicine. The referral criteria to physical and rehabilitation medicine were based on the patients' or parents' complaints of the change in functional capacity or functional decline. Regarding these patients, 12/21 (57.1%) were referred for cardiopulmonary deconditioning and 3/21 (14.3%) had a decrease of autonomy with the inability to independently perform the activities of daily living that they could before the diagnosis. Nineteen patients (19/21, 90.4%) presented a reduction in exercise capacity and, therefore, benefited from a rehabilitation program: seven (7/19, 36.8%) in an outpatient treatment program and 12 (12/19, 63.2%) in a home-based self-controlled exercise program.

A nutritional assessment was also performed in 7/45 patients (15.6%) and three (3/7, 42.8%) were referred to obesity outpatient follow-up, while four (4/7, 57.1%) received instructions on how to improve their nutritional health.

Five patients (5/45, 11.1%) were psychologically assessed, and of those, two were referred to child and adolescent psychiatry. The referral criteria for a psychological assessment were based on the patients' or parents' complaints of anxiety and depressive symptoms related with hospital isolation, an acute period of serious illness, and in some cases, serious sequelae.

DISCUSSION

MIS-C is a severe condition associated with a SARS-CoV-2 infection and evidence is still needed to clarify the various aspects of this syndrome. Our case series focused on describing the clinical presentation and short-term outcomes of this syndrome.

As in previous reports, we found a similar median age (seven years), slight predominance of male patients (68.9%), and most of the patients were previously healthy (68.9%).[14,18-21] Some reports showed that obesity may be a risk factor for MIS-C, but in our case, obesity did not have a statistical association with the severe phenotype of MIS-C.[22]

Current evidence supports a temporal association between a SARS-CoV-2 infection and MIS-C, with MIS-C typically occurring within two to four weeks after an infection or the peak of COVID-19 cases in communities, which is consistent with our case series in which we observed an interval of 33 days from contact with a patient with positive rRT-PCR SARS-CoV-2 to the patient's symptom onset.[7,12,14,19] The high percentage of seropositivity for SARS-CoV-2 with MIS-C, as seen in this case series and other published studies, also supports the hypothesis of MIS-C being a post-infectious presentation of COVID-19 in children.[15,23] Given that a large subset of SARS-CoV-2-infected children display mild to no symptoms, some children may develop MIS-C with little to no advance warning, and in some cases, caregivers may not even be aware that the child was previously infected with SARS-CoV-2.[24]

In our case series, the median duration from symptom onset to hospital admission was six days, a long period of time considering the potential severity of disease. These data allow us to conclude that this syndrome is not always recognized given the possibility of milder presentation but in any case, this syndrome has potentially serious consequences and should motivate close monitoring and hospitalization. To obviate long periods until hospitalization and the management of these patients, it is important to emphasize the importance of a high clinical suspicion of MIS-C in children. In addition, the use of a panel of laboratory tests for inflammation, hypercoagulability, and organ damage might assist in the early identification and management of MIS-C. However, there are no clear data indicating the predictive value for each clinical symptom or laboratory value in diagnosing MIS-C.[25]

Fever and gastrointestinal symptoms, such as diarrhea and abdominal pain, were predominant in the clinical presentation of MIS-C as in other series.[14,15,20] Gastrointestinal manifestations, sometimes mimicking appendicitis or even inflammatory bowel disease were reported to be one of the main presenting clinical features in children with an MIS-C diagnosis.[21,26,27] In agreement with previous reports, we reported three patients in this case series who underwent an appendicectomy following a diagnosis of appendicitis. Differentiating acute appendicitis from abdominal symptoms due to MIS-C may be difficult given the overlap of symptoms but imaging findings and laboratory evaluations could indicate a diagnosis of MIS-C.

Cardiac involvement in previous reports included 71% to 100% of patients and may include an unusual cardiac injury shown by high concentrations of troponin and brain natriuretic peptide, left ventricular dysfunction, coronary artery dilation or coronary artery aneurysm, and electrical conduction abnormalities.[4,7,13-15,20] In this case series, we observed highly elevated troponin and NT-proBNP. In addition, elevated IL-6 levels might also be due to stretched cardiomyocytes and cardiac fibroblasts along with macrophage activation, as these immune cells are the main producers of IL-6.[13] For this reason, cardiac involvement is a hallmark in this syndrome, as observed in our series.[4,7,12,14,18,20,22,28,29] This highlights the importance of monitoring cardiac involvement. Although most patients have markers of cardiac injury, the echocardiogram may not show abnormalities that only a cardiac MRI may identify regarding whether it is an acute injury or cardiac sequelae.

Neurological involvement is reported in other case series, and it is described in up to 20% of affected patients, with varying severity, from irritability and meningismus to severe encephalopathy, which is concordant with our results in which we reported neurological involvement in 15.6% of patients.[30] In addition, we also found that neurological involvement was associated with the severity of MIS-C.

Previous studies reported that a group of patients with MIS-C had a higher incidence of respiratory symptoms and severe respiratory involvement, often requiring intensive care treatment and higher case fatality rates, thereby also satisfying the MIS-C criteria.[31,32] In fact, we observed that respiratory involvement was also associated with the severity of MIS-C in our series.

Regarding management and therapeutic agents, a stepwise approach to immunomodulatory treatment in MIS-C is recommended, but there are insufficient data to compare the efficacy of IVIG and glucocorticoids in MIS-C.[25] We reported 13 patients with severe MIS-C, and of those, six needed methylprednisolone pulses and one anakinra as the second line therapy, as there was therapeutic failure of the first-line drugs.

As also recommended by the literature, all the patients were admitted for observation while the diagnostic evaluation was conducted.[25] Since there were other possible etiological diagnoses, such as malignancy or inflammatory conditions, all the patients underwent additional diagnostic studies and received broad-spectrum antibiotics during hospitalization, until a diagnosis was established, and negative culture results were available.

Because of the high inflammatory state and thrombotic risk based on D-dimer elevation in MIS-C, anticoagulant therapy such as low-molecular-weight heparin (LMWH) is commonly used in these cases.[14,29,33] According to our unit's guidelines, we initiated enoxaparin in prophylactic doses in 17 patients (37.8%) which included patients with severe presentation, prolonged immobilization, and patients with D-dimer elevation that was six-fold the upper limit. Acetylsalicylic acid is also recommended, particularly in MIS-C patients with Kawasaki-like phenotype, coronary artery aneurysms, and thrombocytosis.[25] Also based on our unit's guidelines, we initiated acetylsalicylic acid in anti-platelet doses in 22 patients (48.9%), which included patients who complied with the aforementioned recommendations. Finally, as for vitamin D, it can reduce the risk of infections through several mechanisms such as inducing pathways to lower viral replication rates, reducing concentrations of pro-inflammatory cytokines, and increasing concentrations of anti-inflammatory cytokines.[34] For this reason, evaluation of the vitamin D status has been recommended and correction suggested, and so it is useful to measure the baseline level of serum 25-hydroxyvitamin D at hospital admission.[34] However, further research is needed in this area to confirm the role of vitamin D in MIS-C.[34]

Previous studies showed a mortality rate of 1.7% - 1.8% in MIS-C patients.[21,31] Fortunately, in our case series, there were no deaths. The long-term outcomes of MIS-C remain unknown, but close follow-up is essential given the paucity of knowledge about this syndrome as well as the potential for morbidity gains. Acute cardiac findings are postulated to be a result of cardiac stunning rather than progressive endovascular changes observed in similar conditions, such as Kawasaki disease.[17] Nevertheless, in our case series, eight patients showed abnormalities in the cardiac MRIs and most likely will require long-term treatment. The risk of long-term cardiovascular complications and the approach to monitoring is extrapolated from the follow-up studies of children with Kawasaki disease and viral myocarditis since there is limited data on the post-discharge follow-up of patients with MIS-C. A cardiac MRI may be indicated three to six months after MIS-C diagnosis, especially in patients who presented with moderate-severe left ventricle dysfunction.[35] The usual practice is to limit physical activity for a period until cardiac function fully recovers, which is similar to the practice for children recovering from myocarditis.[36]

Other sequelae following discharge include muscular weakness, reduced exercise capacity, anxiety, and depressive symptoms. Longer-term follow-up will help define the extended natural history of MIS-C.[17] The remarkable reduction in functional exercise capacity in our patients should be attributed to various factors such as the underlying inflammatory nature of the disease, a pre-illness sedentary lifestyle, and the side effects of high-dose corticosteroid use. These factors are in addition to the lack of

physical activity opportunities for all young people during the COVID-19 pandemic.

MIS-C is still characterized by the scarcity of information regarding its etiology, pathophysiology, and long-term outcomes which impairs the optimal management of these patients. Furthermore, this syndrome represents potentially severe medical sequelae which, despite its rarity, enhances not only the importance of additional research but also of COVID-19 mitigation efforts to prevent the transmission of SARS-CoV-2 and, consequently, MIS-C.[24]

The early identification of MIS-C is essential for a timely approach to the disease, and for that reason, studies comparing MIS-C patients to other patients hospitalized with SARS-CoV-2 will be useful in identifying the possible predictors for the early diagnosis of MIS-C.

There are other questions about MIS-C that remain unanswered including management and optimal treatment, which disclose the importance of future randomized clinical trials and of reporting this syndrome globally to provide better care for patients.

CONCLUSION

We observed a large spectrum of disease presentation, and most patients were previously healthy. A small percentage of patients (28.9%) had a severe presentation of the disease. Nonetheless, even those patients had a good short-term outcome since we did not report any deaths in our case series. Despite that, the long-term outcomes could be an important burden on children's health. In fact, we observed several cardiac, physical, and psychological sequelae, and for that reason, it is important to emphasize that these patients should have a long follow-up with a particular focus on cardiac involvement since it is a hallmark in MIS-C.

AUTHOR CONTRIBUTIONS

JVM, RV: Data collection, analysis, and interpretation; draft of the paper; critical review of the paper.

AMG, TS, CG: Data analysis and interpretation; review of the paper.

MJB: Data analysis and interpretation; critical review of the paper.

All the authors read and approved the final manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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The National Response to Patients with Acute Coronary Syndrome during the First Wave of the COVID-19 Pandemic in Portugal

A Resposta Portuguesa na Síndrome Coronária Aguda durante a Primeira Onda da Pandemia de COVID-19

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to changes in healthcare institutions and medical assistance. Non-SARS-CoV-2 related diseases were indirectly affected by the pandemic. Nonetheless, their treatment remains crucial. Cardiovascular conditions such as acute coronary syndrome (ACS) are common, and it was necessary to adjust medical assistance to these diseases during the pandemic. This study aimed to assess the national impact and healthcare system response during the first wave of the pandemic in patients admitted for ACS.

Material and Methods: Multicenter retrospective study based on the Acute Coronary Syndrome Portuguese National Registry between the 1st January 2016 and the 28th February 2021. Two groups were defined: the previous year to the SARS-CoV-2 pandemic (March, April, May and June 2019) (952 patients) and the first wave of the pandemic (March, April, May and June 2020) (642 patients). Clinical course, time until reperfusion, in-hospital outcomes and follow-up at one year were compared between both periods.

Results: There was a lower incidence of ACS between March and June 2020 compared with the same period in 2019, with a reduction of 32.6%. There were no statistically significant differences between the two periods regarding patient demographic characteristics (except for a higher prevalence of familiar cardiovascular history and chronic obstructive pulmonary disease in 2020 and higher prevalence of diabetes in 2019), clinical features, clinical management, in-hospital major adverse cardiac events, mortality and readmission at one-year follow-up. There was a trend towards longer delays until reperfusion, yet without statistical significance. The patients that developed ACS during the first wave of the SARS-CoV-2 pandemic were less often referred to percutaneous coronary intervention centers ($p = 0.034$) and were more frequently transferred to another hospital ($p < 0.001$).

Conclusion: During the first wave of the SARS-CoV-2 pandemic there was a nationwide reduction in demand of healthcare services due to ACS events. Even though the Portuguese healthcare system was under strain and forced to divert resources and medical assistance towards the pandemic management, it was capable of responding adequately to ACS.

Keywords: Acute Coronary Syndrome; COVID-19; Pandemics; Portugal; SARS-CoV-2

RESUMO

Introdução: O *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2) condicionou drásticas alterações nas instituições de saúde e assistência médica. Doenças não relacionadas com SARS-CoV-2 foram indiretamente afetadas pela pandemia, apesar de o seu tratamento se manter fundamental. As doenças cardiovasculares, como a síndrome coronária aguda (SCA), são prevalentes e foi necessário adaptar a assistência a estas doenças durante a pandemia. Este estudo tem como objetivo avaliar o impacto nacional e a resposta das instituições de saúde durante a primeira onda da pandemia em doentes admitidos por SCA.

Material e Métodos: Estudo retrospetivo multicêntrico com dados do Registo Nacional Português de síndrome coronária aguda entre 1 de janeiro de 2016 e 28 de fevereiro de 2021. Foram definidos dois grupos: o ano anterior ao ano da pandemia (março, abril, maio e junho 2019) (952 doentes) e a primeira onda da pandemia (março, abril, maio e junho 2020) (642 doentes). Características clínicas, tempo até à reperfusão, complicações intra-hospitalares e seguimento a um ano foram comparados entre os dois períodos.

Resultados: Nos meses de 2020 registou-se uma menor incidência de SCA comparando com o mesmo período em 2019, com uma redução de 32,6%. Não se registaram diferenças estatisticamente significativas entre os dois períodos temporais no que diz respeito às características demográficas e clínicas (exceto pela maior prevalência de doença cardiovascular familiar e doença pulmonar obstrutiva crónica em 2020, e maior prevalência de diabetes em 2019), abordagem clínica, complicações intra-hospitalares e mortalidade e readmissão durante o seguimento a um ano. Verificou-se uma tendência para um atraso até à reperfusão, sem significância estatística. Os doentes com SCA durante a pandemia foram menos referenciados para centros com intervenção coronária percutânea ($p = 0,034$) e foram mais frequentemente transferidos para outro hospital ($p < 0,001$).

Conclusão: Durante a primeira onda da pandemia de COVID-19 registou-se uma redução nas hospitalizações por SCA. O sistema nacional de saúde português esteve sob pressão e stresse para prestar assistência durante a pandemia. No entanto foi capaz de fornecer uma resposta adequada aos doentes admitidos por SCA.

Palavras-chave: COVID-19; Pandemia; Portugal; SARS-CoV-2; Síndrome Coronária Aguda

INTRODUCTION

In 2020 the world was confronted with a new pandemic, a highly contagious and deadly virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization, over 583 million people were infected and more than 6,4 million deaths were registered,[1] with a mortality rate of approximately 2%.

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When confronted with the pandemic, all countries were forced to implement several measures to mitigate the impact of the SARS-CoV-2 infection. Portugal started by proposing several individual limitations and social distancing measures. However, it ended up enforcing a national lockdown on the 18th March 2020, where individuals stayed in home confinement except for essential reasons.[2] These measures were essential to contain the pandemic progression and allow the healthcare system to become capable of confronting an unknown and aggressive infection.

The absence of curative or preventive medical treatments at the time caused a significant strain to the healthcare system, by demanding large support from intensive care units and dedicated healthcare professionals. These changes led to a reorganization and restructuring of the resources within the hospitals,[3] the cancelation of non-essential procedures and outpatient clinic appointments to allow the healthcare system to be able to respond to the SARS-CoV-2 infection without neglecting the medical management of prevalent non-SARS-CoV-2 diseases.

The true effect of this pandemic on non-SARS-CoV-2 patients has been difficult to quantify. During the pandemic, physicians raised concerns regarding the reduction of emergency admissions and diagnosis of severe acute conditions, as well as a higher incidence of sudden cardiac arrest.[4] Some of these cases can be a consequence of acute coronary syndrome (ACS) and the delay in its approach and treatment. ACS is a highly prevalent condition that involves a life-saving evidence-based emergent treatment.[5] Worldwide, incidence reports of ACS significantly decreased during the pandemic period.[6-10] A reduction in the diagnosis and treatment of ACS can lead to severe long-term consequences in the Portuguese population. Several explanations were proposed for the reduction of severe acute disease in the emergency department. Some experts postulated that the reduction of ACS incidence was due to the patients' fear of being infected with SARS-CoV-2 in healthcare facilities, an increase in patients' threshold for calling emergency services and a reduction of the capacity of the healthcare system to provide individual attention.[11,12]

Based on previous reports and the overall Portuguese healthcare system support during the SARS-CoV-2 pandemic, our goal was to understand if there were changes in the response of the national healthcare care system to patients with ACS and if the profile of ACS patients during the pandemic period was different from previous years.

MATERIAL AND METHODS

Pro-ACS registry design

The Portuguese Registry of Acute Coronary Syndromes (Pro-ACS– ClinicalTrials.gov NCT 0162329) is a continuous, nationwide, prospective, observational registry launched in 2002. Data is uploaded by participating centers and managed by the Portuguese Society of Cardiology. All ACS patients older than 18 years are eligible for inclusion. ACS episodes are adjudicated according to current guidelines and based on electrocardiogram, myocardial necrosis biomarkers and clinical status.[13] Data collected include patient demographics, baseline characteristics, presenting symptoms, biochemical, electro and echocardiography findings, clinical evolution, medical treatment (background, in-hospital and post-discharge), coronary anatomy, revascularization procedures, and clinical outcomes. Outcome data were collected after hospital discharge and after one-year of follow-up.

Study population

A total of 13 950 validated episodes in the Pro-ACS registry between the 1st January 2016 and the 28th February 2021 were accessed. Considering the seasonality of ACS, we started by comparing the occurrence of ACS between March, April, May and June 2016, 2017, 2018, 2019 and 2020. Then we compared these months in 2020 with the same period in 2019. Finally, we compared the first SARS-CoV-2 wave (between March and June 2020) with the second and third waves (November - December 2020, and January - February 2021).

Each patient might have had more than one episode of ACS. Patients with missing data regarding the ACS type and times until medical care were excluded. ACS episodes were classified according to the Fourth Universal Definition of Myocardial Infarction.[13] Then, patients were categorized in the final diagnosis of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina.

Multivessel disease was defined as the presence of two or more coronary artery stenosis (> 50%). Valvular heart disease was defined as severe valvular stenosis or regurgitation or previous valvular intervention. Family history of cardiovascular disease refers to patients with at least one relative that presented a previous cardiac event (including sudden cardiac arrest) before the age of 65. Chronic kidney disease was considered in all the patients with a creatinine level higher than 2 mg/dL or glomerular filtration rate below 30 mL/min/1.73 m^2. Hybrid revascularization was defined as the revascularization technique that combines both percutaneous coronary intervention and coronary artery bypass.

Ethics committee approval

Participation in the registry must be approved by the institutional review board at each institution, the local ethics committee and the Portuguese Data Protection Authority (no. 3140/2010).[14] All ethical requirements in the Helsinki Declaration 2013 were met, not involving any human and/or animal experimentation. Written informed consent for the introduction of patient' data into the registry is available since 2010 and has been applied after approval by the ethics committee of each hospital center.

Statistical analysis

All statistical analyses were performed by a professional statistician within the National Centre for Data Collection in Cardiology (CNCDC), using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows XP (version 20.0).

The groups were characterized according to continuous and categorical variables. Continuous variables being expressed as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) in case of skewed distribution. Comparisons between groups regarding categorical variables were conducted using the chi-square test or Fisher's test. Means of continuous variables were compared using *t* tests whenever possible; otherwise, the Mann-Whitney U test was used to compare the medians. When more than two groups were analyzed together, the chi-square test or the Monte Carlo simulation test for the chi-square statistic was used for categorical variables and analysis of variance or the Kruskal-Wallis test was used for continuous variables. Significance level of 5% was assumed for testing the hypothesis.

RESULTS

Regarding the evaluation of the years before the SARS-CoV-2 pandemic, between March, April, May and June 2016, 2017, 2018, 2019 and 2020, there was a fluctuating incidence of ACS (Fig. 1). Nonetheless, patients admitted with ACS in these periods presented similar baseline demographic, clinical course as well as clinical outcomes. Table 1 in Appendix 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18610/Appendix_01.pdf) displays the differences according to the year. Over the years, there was an improvement in STEMI patient referral directly to the catheterization laboratory, as well as an overall reduction in the admission for ACS in centers without percutaneous coronary intervention capacity (PCI).

A total of 952 ACS events were registered during those months in 2019, while the same period in 2020 recorded only 642. This represented a significant reduction of 32.6% in the number of ACS events reported at a national level during the first pandemic wave. On the other hand, the relative proportion of types of ACS remained similar (STEMI 53.7% *vs* 51.6%, $p = 0.406$; NSTEMI 43.6% *vs* 46.1%, $p = 0.322$).

Patients admitted for ACS prior the SARS-CoV-2 pandemic and during the pandemic were similar regarding demographic characteristics, as represented in Table 1. The prevalence of cardiovascular risk factors was similar, except for diabetes mellitus (31.9% *vs* 26.4%, $p = 0.023$). Concerning other comorbidities, only chronic obstructive pulmonary disease revealed a higher prevalence in 2020 (3.5% *vs* 6.3%, $p = 0.019$).

Table 2 illustrates the clinical presentation features in the two periods considered, and no significant differences were found. The pandemic group was more frequently admitted to hospitals without a catheterization laboratory ($p = 0.034$) and, consequently, the rates of transfer to another hospital were higher ($p < 0.001$). Other patterns of hospital admission did not change significantly from 2019 to 2020. Nevertheless, a trend towards a reduction of direct transfers from the pre-hospital emergency medical services to a PCI center ($p = 0.090$) was noticed. Concerning all times for assistance of ACS during the pandemic, there was a trend towards a longer delay in seeking hospital admission despite no significant delays being recorded, transfer delays and longer times until admission and reperfusion were also detected during the pandemic period.

Regarding the clinical management (Table 3) no significant differences were reported between the SARS-CoV-2 year and the previous year. The exception were patients undergoing coronary angiography, which was more frequent during the SARS-CoV-2 period ($p < 0.001$). No differences were observed regarding revascularization strategy, multivessel disease prevalence, intervention performance and

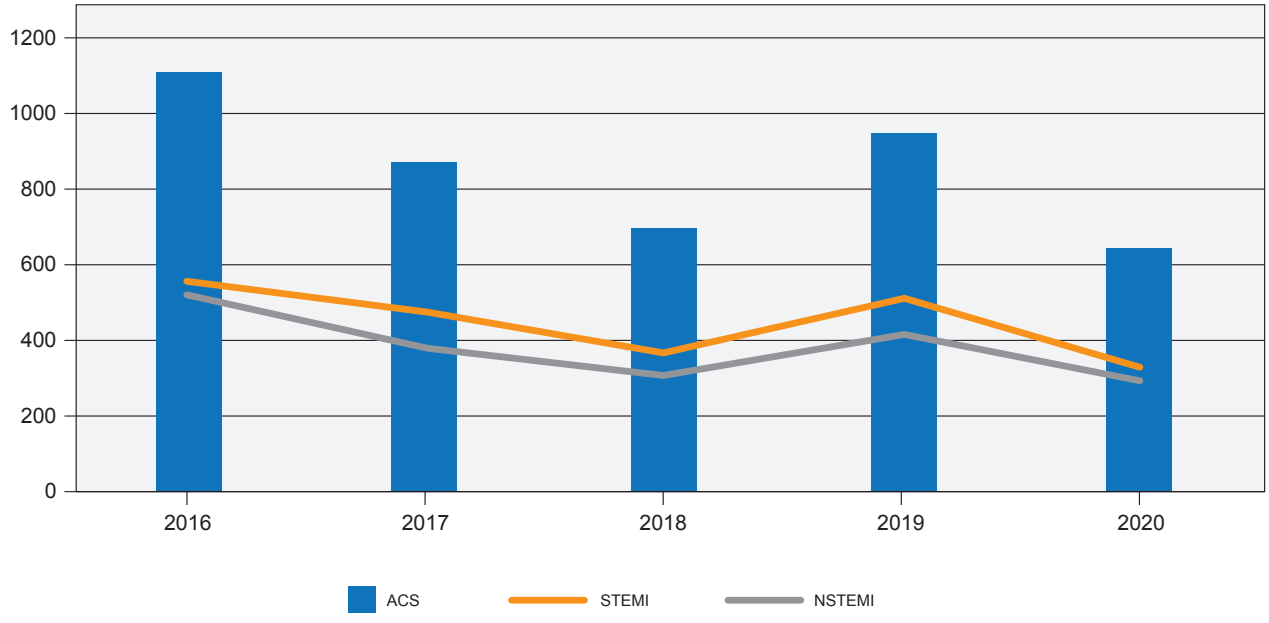

Figure 1 – The incidence of acute coronary syndromes (ACS) in the months of March, April, May and June according to the year
STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction

Table 1 – Demographic characteristics of the patients admitted for acute coronary syndrome according to the year

	2019 (n = 952)	2020 (n = 642)	*p*-value
Age, years	66 ± 13	65 ± 13	0.207
Sex, (male)	708 (74.4%)	499 (77.7%)	0.125
Smoking, n (%)	242 (32.1%)	189 (37.1%)	0.066
Arterial hypertension, n (%)	620 (67.6%)	396 (65.3%)	0.359
Diabetes mellitus, n (%)	277 (31.9%)	160 (26.4%)	0.025
Dyslipidaemia, n (%)	507 (55.3%)	318 (52.6%)	0.296
Familiar cardiovascular history, n (%)	22 (2.4%)	26 (4.5%)	0.023
Angina, n (%)	188 (24.6%)	100 (21.6%)	0.223
Previous ACS, n (%)	132 (16.5%)	87 (18.8%)	0.292
Valvular heart disease, n (%)	18 (2.2%)	13 (2.8%)	0.526
Previous heart failure, n (%)	50 (6.2%)	32 (6.9%)	0.621
Peripheral arterial disease, n (%)	32 (4.0%)	19 (4.1%)	0.907
Chronic kidney disease, n (%)	63 (7.9%)	29 (6.3%)	0.310
Cancer, n (%)	35 (4.4%)	23 (5.0%)	0.601
Chronic obstructive pulmonary disease, n (%)	28 (3.5%)	29 (6.3%)	0.019
Dementia, n (%)	12 (1.5%)	7 (1.5%)	0.970
Previous bleeding, n (%)	16 (2.0%)	8 (1.8%)	0.756

Table 2 – Clinical presentation characteristics of the patients admitted for acute coronary syndrome according to the year

	2019 (n = 952)	2020 (n = 642)	*p*-value
Chest pain, n (%)	695 (92.5%)	462 (94.5%)	0.183
Dyspnoea, n (%)	16 (2.1%)	9 (1.8%)	0.723
Cardiac arrest, n (%)	6 (0.8%)	3 (0.6%)	1.000
Killip-Kimball class > I, n (%)	133 (16.9%)	72 (15.5%)	0.515
ST-elevation myocardial infarction, n (%)	511 (53.7%)	331 (51.6%)	0.406
Non-ST-elevation myocardial infarction, n (%)	415 (43.6%)	296 (46.1%)	0.322
Pre-hospital emergency medical service, n (%)	211 (22.8%)	111 (19.1%)	0.090
Transfer to another hospital, n (%)	143 (15.4%)	152 (26.2%)	< 0.001
Non-percutaneous coronary intervention capable hospital, n (%)	242 (26.6%)	183 (31.7%)	0.034
Time from the onset of symptoms to first medical contact, (min) (median, IQR)	188 (92, 409)	171 (93, 352)	0.362
Time from the first medical contact to hospital admission, (min) (median, IQR)	152 (60, 381)	175 (60, 388)	0.838
Time from the onset of symptoms to reperfusion, (min) (median, IQR)	251 (180, 374)	285 (210, 443)	0.110
Time from the first medical contact to reperfusion, (min) (median, IQR)	105 (60, 168)	106 (57, 171)	0.773
Time from door to reperfusion, (min) (median, IQR)	64 (30, 117)	60 (30, 160)	0.773

min: minutes; IQR: interquartile range

the success rates of all interventions.

During the pandemic, no differences were found concerning re-infarction, heart failure, new onset of atrial fibrillation, cardiogenic shock, mechanical complications, cardiac arrest, stroke, major bleeding and in-hospital all-cause of death (Table 4) between 2019 and 2020. Nonetheless, during the four months of 2020 we noted a higher incidence of atrioventricular block (1.4 *vs* 3.5%, $p = 0.010$) and sustained ventricular tachycardia (0.4 *vs* 1.9%, $p = 0.012$). During these patient's short follow-up period of one year (129 patients with follow-up, 90 in 2019 and 39 in 2020), the pandemic group had a higher incidence of death (10.0 *vs* 20.5%, $p = 0.105$) and readmission for all causes (7.4 *vs* 10.5%, $p = 0.724$) even though without statistical significance.

When comparing the first pandemic peak (March to June 2020) to the second and third peaks in Portugal (November, December 2020 and January, February 2021) no significant differences were found regarding the incidence of ACS, STEMI, all-time components, in-hospital outcomes, in-hospital mortality, readmission for all causes and mortality rates at one-year follow-up [Appendix 1, Table 2 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18610/Appendix_01.pdf)]. Nonetheless a

Table 3 – Clinical management, angiography and revascularization characteristics of the patients admitted for acute coronary syndrome according to the year

	2019 (n = 952)	2020 (n = 642)	*p*-value
Left ventricular ejection function, (%)	50 ± 10	51 ± 10	0.299
Angiography performance, n (%)	573 (60.3%)	494 (77.1%)	< 0.001
Radial access, n (%)	880 (92.5%)	570 (88.9%)	0.093
Multivessel disease, n (%)	328 (34.5%)	247 (38.5%)	0.199
Percutaneous coronary intervention, n (%)	485 (51.2%)	430 (67.3%)	< 0.001
Coronary artery bypass grafting, n (%)	25 (7.6%)	14 (4.3%)	0.074

Table 4 – In-hospital complications of the patients admitted for acute coronary syndrome according to the year

	2019 (n = 952)	2020 (n = 642)	*p*-value
Mortality, n (%)	39 (4.1%)	27 (4.3%)	0.830
Major adverse cardiac events, n (%)	137 (14.4%)	107 (16.8%)	0.244
Reinfarction, n (%)	5 (0.5%)	1 (0.2%)	0.422
Heart failure, n (%)	80 (8.4%)	57 (9.0%)	0.751
Cardiogenic shock, n (%)	26 (2.8%)	14 (2.2%)	0.477
New-onset atrial fibrillation, n (%)	40 (4.2%)	37 (5.8%)	0.173
Mechanical complication, n (%)	2 (0.2%)	0 (0.0%)	0.533
Complete atrioventricular block, n (%)	13 (1.4%)	22 (3.5%)	0.010
Sustained ventricular tachycardia, n (%)	4 (0.4%)	12 (1.9%)	0.012
Cardiac arrest, n (%)	27 (2.9%)	25 (4.0%)	0.321
Stroke, n (%)	6 (0.6%)	4 (0.8%)	0.733
Major haemorrhagic events, n (%)	4 (0.4%)	8 (1.3%)	0.082

higher incidence of diabetes patients and patients admitted in the emergency room in the second and third waves were observed. Moreover, the first wave had a better angiography and percutaneous coronary intervention performance, as well as a higher rates of transfer to another hospital.

DISCUSSION

In this study we found a nationwide reduction of 32.6% in demand of healthcare services due to ACS events during the first wave of SARS-CoV-2 infection. Also, during this period, patients were less often referred to percutaneous coronary intervention centers. Nonetheless, the overall Portuguese healthcare system was capable of responding adequately to ACS during the pandemic.

The SARS-CoV-2 pandemic caused significant strain to the healthcare system all around the world. Yet, most of the studies during this period argued that the SARS-CoV-2 impact was only modest and did not overload the healthcare system.[15] However, this impact can also play a role on the decline of ACS incidence. Some patients did avoid accessing the healthcare system by fear of getting infected, and the strict measures applied by national authorities may have contributed to a reduction in the number of emergency admissions[16] and, as a consequence, a reduction in hospital admissions due to non-related SARS-CoV-2 diseases, notably ACS.[9,17,18] A different explanation for the reduction of ACS during the pandemic argues that different factors like a decline in atmospheric pollution, a reduction in physical activity and other radical adjustments due to the lockdown were capable of influencing the atherosclerotic plaques and promote its stabilization.[19] The present analysis is not capable of considering the factors presented in the last hypothesis.

Portugal was no different from most countries, as a decrease in emergency admissions and an increase of the overall mortality rate during the first SARS-CoV-2 wave was found. Nonetheless, this increase in the mortality rates was possibly not entirely related with the SARS-CoV-2 infection,[20] thus strengthening the importance of establishing efficient health policies to manage non-related SARS-CoV-2 disease. In this national database, we reported a lower nationwide incidence of ACS admissions. However, the pandemic ACS patients did not present major differences regarding their characteristics, management and prognosis in comparison with the same period in the previous year.

National and international publications corroborate our findings of a substantial reduction in the incidence of ACS[4,21-23] in 2020. Moreover, the pandemic led to a reduction in hospitalizations due to coronary artery disease, cardiac diagnostic procedures, PCI and structural interventions worldwide.[23] Many Portuguese centers described the impact of the pandemic on their healthcare assistance, namely its impact on STEMI patients.[24,25] Moreover, different authors reported a more substantial reduction in the incidence of

NSTEMI over STEMI.[10,26] Our data reported an overall reduction of ACS events, with an absolute decrease of all types of ACS at a national level, although the proportions of the ACS subtypes remained the same. The demographic characteristics of patients were similar and coronary artery disease had the same severity between the two periods, which is in agreement with previous reports from various Portuguese regions.[24,27] Nonetheless, without mortality data from the non-SARS-CoV-2 patients, we still do not know if there was a real reduction in ACS incidence or just a reduction of ACS admissions secondary to decreased demand for medical assistance.

The pressure in the healthcare system was so overwhelming in some regions of the world that these regions had to adjust the reperfusion strategy in ACS, and implemented fibrinolysis protocols over percutaneous coronary intervention as the first measure in case of STEMI patients.[28] This was not the case in Portugal since no differences in reperfusion strategies were found in the national database or other national series.[24,25,27] Also, no differences were reported concerning the clinical presentation and management of the ACS between the two periods.

Our results demonstrated the absence of delays regarding all times to medical assistance and reperfusion in the pandemic context, which is in line with several series of Portuguese healthcare institutions, although a trend towards a delay during the pandemic was observed.[24,25,27] Other countries reported different outcomes, given some countries were able to maintain the times from the onset of symptoms until reperfusion[29,30] while others presented a delay.[22] Therefore, in Portugal, the overall provision of medical assistance and reperfusion did not seem to have been influenced by the SARS-CoV-2 pandemic, probably because the Portuguese healthcare system did not collapse[31] during the first wave of the pandemic.

A significant number of patients was not directly referred to a hospital with PCI capacity which favors the system delay and overload, since it implies a logistic effort to transfer the patient, and forcing healthcare professionals to adopt protective measures during the transfer and during PCI, with both healthcare institutions needing to have a dedicated area to receive these patients, thus extending the time until the reperfusion. This was an issue our database did not explore, but nonetheless was mentioned by other colleagues in one Portuguese region.[25]

Prognosis, in-hospital mortality and in-hospital complications were more prevalent in the pandemic group, but without statistically significant differences. Other authors reported similar findings,[17,25,27] which suggest that Portugal's public health measures were able to maintain primary care services for ACS patients. Even so, some authors from Portuguese healthcare institutions presented different results, with a higher incidence of mechanical ACS complications and in-hospital mortality.[24] Nonetheless, if we consider the reduction in the number of documented ACS events nationwide, it's possible that the prognosis of the patients properly identified as ACS during the pandemic is the same as the patients in the previous years. If we consider that the reduction of ACS events may be due to patients avoiding healthcare systems, the overall prognosis of ACS may be worse than perceived, given that eventually patients without proper assistance during the acute event may develop heart failure and other late complications. These complications, which would probably be avoided or attenuated by diagnosis and prompt treatment, may result in higher costs, either for both the healthcare systems (monetary costs) and for patients (poorer quality of life, higher morbidity and mortality).

In the first pandemic wave, the Portuguese healthcare system was capable of responding without the entire system collapsing, given that the incidence of SARS-CoV-2 infection was lower than in other countries. With the second and third waves, a reorganization of the emergency and of other departments was required to be able to respond to the overload of SARS-CoV-2 patients. New circuits and more healthcare professionals were recruited to carry out different assignments from their everyday practice to support their colleagues, something that further compromised the ability to provide care to patients with non-related SARS-CoV-2 diseases.

Health authorities were crucial in the prompt and efficient ACS response. Since the first SARS-CoV-2 pandemic wave, health authorities developed campaigns to ensure the safety of the healthcare institutions in managing other diseases and that medical assistance to ACS was safe and with a low risk of infection.[24] This may explain why the response to ACS care during the second and third waves was similar to the first wave. Although those waves were worse in terms of number of infections and overload of resources, the in-hospital outcomes were similar to those of the first wave. A reduction of the overall number of ACS events was also recorded in these waves compared to numbers prior to the pandemic.

This study described the nationwide management of ACS during the first three pandemic SARS-CoV-2 waves in Portugal. It showed that the healthcare system was able to provide high-quality cardiovascular care to the population. Nonetheless, continuous cardiovascular educational programs are crucial in order to maintain this level of care, since it's possible that in coming years an increasing number of patients might attend the emergency department as a consequence of ACS that was not treated during the SARS-CoV-2 pandemic. Moreover, this experience could be beneficial to establish new protocols and as preparation in case of future pandemics.

Limitations

There are several limitations to be considered in the study design and interpretation.

This was an observational and non-randomized study, which can have associated confounders that can influence the outcomes. Some of the patients could have misclassified characteristics or incomplete records. The analysis of differences between patients with and without the combined

endpoint was performed with univariable, non-adjusted models without correction of multiple inferential tests. Acute morbidity and mortality could have been underestimated since the pre-hospital care was not considered, and we did not have data from these patients. If we had had access to all the autopsies in these periods, we would also be able to further understand if the excess of unexplained mortality was related to undetected ACS or not.

Other complications, namely non-cardiovascular complications, could have interfered with the patient's prognosis, but were not considered in the registry. Even considering the high number of patients in the registry, only a few patients had a documented follow-up after the hospitalization.

This study did not evaluate the potential relationship between the presence of SARS-CoV-2 infection and a concomitant occurrence of ACS.

CONCLUSION

During the first wave of the SARS-CoV-2 pandemic waves there was a reduction in the incidence of ACS, including STEMI and NSTEMI. The Portuguese system was able to provide adequate assistance to patients with ACS. Further research is needed to understand the causes that were associated with the reduction in the number of ACS admissions during the first wave of SARS-CoV-2 pandemic and the long-term repercussion of the pandemic on cardiovascular health.

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AUTHOR CONTRIBUTIONS

HS: Writing of the manuscript.

MS, SBP: Statistical analysis, revision of the manuscript.

IA, SA, LA: Critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Cutaneous Markers of Cardiovascular Diseases

Manifestações Cutâneas das Doenças Cardiovasculares

ARTIGO DE REVISÃO

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ABSTRACT

Cardiovascular diseases are one of the most important global medical challenges because of their high rates of morbidity and mortality. In this narrative review, the authors address the most important dermatologic signs that can be present in patients with cardiovascular disease. The early recognition of these underestimated entities is very important as it may lead to an early diagnosis and timely treatment, thus lessening the effects of long-term disease and possibly improving the prognosis.
Keywords: Cardiovascular Diseases; Skin Manifestations

RESUMO

As doenças cardiovasculares são um dos desafios médicos mais importantes a nível mundial devido às suas elevadas taxas de morbilidade e mortalidade. Neste artigo, é feita uma revisão das manifestações cutâneas mais importantes que poderão estar presentes em doentes com doenças cardiovasculares. O reconhecimento atempado destas entidades clínicas é fulcral, uma vez que permite um diagnóstico e tratamento precoces, minimizando os efeitos destas doenças a longo prazo e possivelmente melhorando o prognóstico destes doentes.
Palavras-chave: Doenças Cardiovasculares; Manifestações Cutâneas

INTRODUCTION

Cardiovascular diseases (CVD) are considered a global priority because of their high rates of morbidity and mortality. Current epidemiologic predictions show that the burden of CVD is increasing significantly, and that only 2% to 7% of the population have no cardiovascular risk.[1] A good amount of information about CVD can be obtained through inspection of the patient, which is a frequently overlooked aspect.[2] General practitioners, internists and dermatologists may frequently be the first physicians to suspect a diagnosis of an underlying CVD by identification of certain cutaneous abnormalities.[3–5] The prompt recognition of these skin manifestations may lead to an early diagnosis and timely treatment, which would then mitigate the effects of long-term disease and improve the prognosis.

This article aims at providing an overview of the dermatologic signs of CVD, including multisystem disorders and inherited diseases that can affect both the heart and the skin, in addition to cutaneous abnormalities due to cardiovascular therapeutics.

GENERAL DERMATOLOGIC SIGNS OF CARDIOVASCULAR DISEASE

Edema

Edema results from accumulation of excessive fluid in the interstitial space.[3] Chronic bilateral peripheral edema is located in dependent areas such as the feet and the lower legs, and the sacral region in bedridden patients. It is usually caused by right-sided heart failure (HF),[6,7] regardless of its cause,[3] or chronic venous insufficiency,[6] which would be suggested by the presence of varicosities and stasis dermatitis.[8] Acute unilateral edema of the limbs is usually caused by local venous obstruction,[2] as in deep venous thrombosis.[9] Edema of the head, neck and upper extremities is seen in superior vena cava syndrome, subclavian vein thrombosis, or lymphatic obstruction.[2]

Cyanosis

Cyanosis is a bluish discoloration of the skin that occurs when there is at least 5 g/dL of deoxygenated hemoglobin. Cyanosis may be central or peripheral.[2–4] Central cyanosis is the result of an abnormal hemoglobin derivative or decreased arterial oxygen saturation (intracardiac right-to-left shunts or intrapulmonary shunts).[10] Therefore, both the mucous membranes and the skin are affected.[2–4] Peripheral cyanosis occurs in patients with normal arterial oxygen saturation, but with decreased blood flow and increased oxygen extraction, and is caused by cold exposure, shock, HF and peripheral vascular disease (PVD). This type of cyanosis is detected on the nose, lips, earlobes, and fingertips,[2,5] but the mucous membranes are spared.[4,10] Differential cyanosis involving the lower extremities, but sparing the upper extremities, may occur in patients with patent ductus arteriosus.[4]

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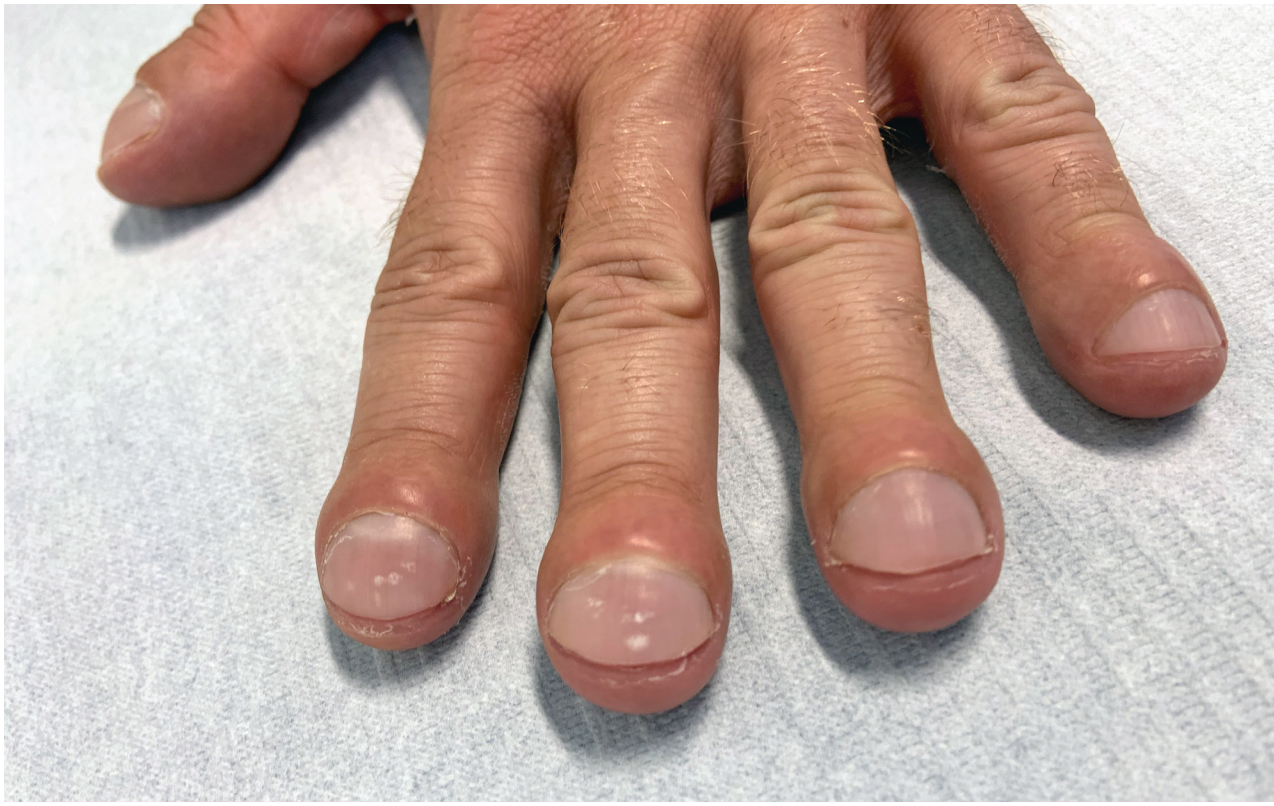

Figure 1 – Digital clubbing: watch-glass nails and drumstick fingers

Digital clubbing

Clubbing is characterized by 'watch-glass nails' and drumstick fingers (Fig. 1).[2,3] The angle between the nail and the cuticle (Lovibond's angle) becomes convex and the window between the thumbnails when held together in profile is lost (Schamroth's sign).[2,11] Digital clubbing is characterized by proliferation of the connective tissue between the nail matrix and the distal phalange[4] and is associated with cyanotic congenital heart disease (left-to-right shunts such as tetralogy of Fallot and transposition of the great vessels), myxoma of the left atrium and subacute bacterial endocarditis.[4,11] Differential clubbing (present on the toes but not fingers) can be seen in patients with patent ductus arteriosus.[2]

DERMATOLOGIC MANIFESTATIONS OF SPECIFIC CARDIOVASCULAR DISEASES

1. Coronary artery disease

Coronary artery disease (CAD) is rapidly increasing in prevalence around the world and is the leading cause of death in developed and developing countries.[12] Certain cutaneous markers are associated with atherosclerosis and can help identify early asymptomatic CAD in high-risk individuals.[13]

Hyperlipoproteinemia and xanthomas

Xanthomas are localized lipid infiltrates found in the skin, tendons and fascia, and are frequently the first sign of hyperlipidemia, especially familial forms.[14] Their recognition should lead to laboratory evaluation of cholesterol and triglyceride levels,[3] as they can be associated with accelerated atherosclerosis and myocardial infarctions.[4] There are several types of xanthomas. Plane xanthomas are soft yellow plaques that occur on the neck, palms (palmar crease xanthomas), and eyelids (xanthelasmas).[3,4,13,14] Tendinous xanthomas are painless nodules most frequently involving the Achilles' tendons, extensor tendons of the elbows and knees.[3] Tuberous xanthomas are yellow painless nodules of the elbows, knees, knuckles, buttocks, and heels. They are softer than tendinous xanthomas and not attached to the tendon.[3] Eruptive xanthomas are associated with uncontrolled diabetes mellitus and hypertriglyceridemia,[15] and appear as a sudden eruption of multiple erythematous-yellow dome-shaped papules involving the extensor surfaces of the extremities and buttocks. They tend to regress rapidly upon treatment.[3,4]

Earlobe crease

The association between earlobe crease (Frank's sign) and CAD remains controversial.[3,4,16] Some studies suggest that the earlobe crease is merely a result of aging,[17] while others propose that it is an independent marker of CAD, conferring increased risk of acute myocardial infarction and cardiovascular death.[3,18,19] Clinically, it is an acquired diagonal deep wrinkle in the lobar portion of one or both auricles.[14] Although the pathogenesis remains unknown, biopsies of the earlobe demonstrated small artery arteriosclerosis and generalized elastin loss. These findings may support that the ear lobe crease is a sign of microvascular disease with occlusion of end-arteries, such as in the earlobes and heart.[19]

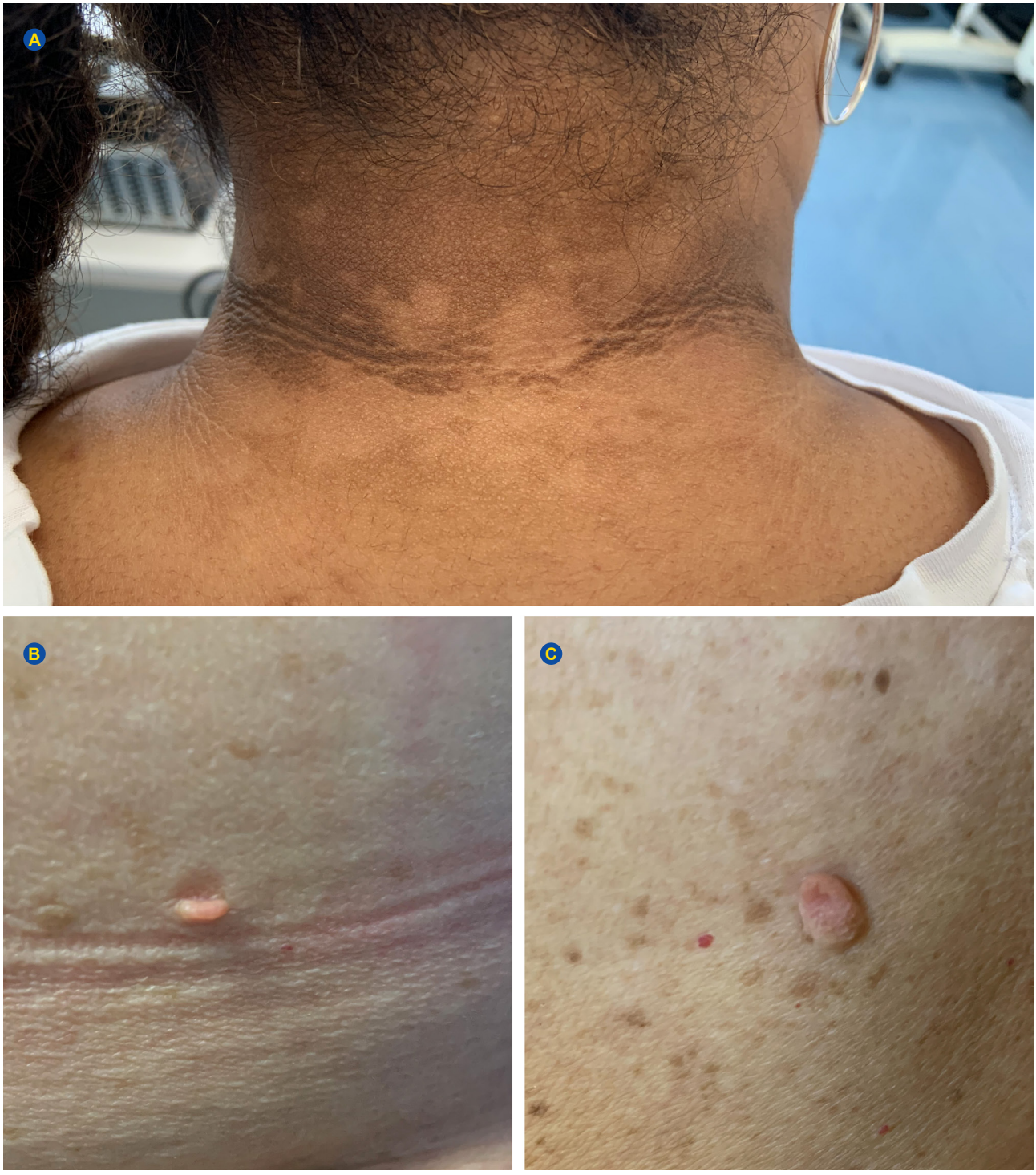

Figure 2 – (A) Acanthosis nigricans: thickened, dark brown, velvety plaques on the posterior aspect of the neck; (B and C) Skin tags (soft fibromas): small, soft skin color papules and nodules over the lateral aspects of the trunk.

Acanthosis nigricans

Acanthosis nigricans (Fig. 2A) is characterized by dark brown velvety and papillomatous plaques in the neck and intertriginous areas.[15] Acanthosis nigricans is not a disease *per se*, but a cutaneous sign of insulin resistance, diabetes and metabolic syndrome, which are great risk factors for CAD. The recognition of this cutaneous sign should lead to a prompt cardiovascular assessment.[13,20]

Skin tags

Skin tags or soft fibromas (Figs. 2B and 2C) are the most common fibroepithelial tumors of the skin. Clinically, they are small, soft tumors appearing over the lateral aspects of the neck, back, axilla, and trunk. Some studies found an association with hypertension, hyperlipidemia, insulin resistance and diabetes.[20]

2. Valvular diseases

Mitral valve stenosis

Mitral stenosis is characterized by narrowing of the valve orifice. In advanced disease, patients may have a malar flush, with plethoric cheeks, punctuated by blueish patches: the typical 'mitral facies', which is probably related with impaired cardiac output.[4,21]

Aortic valve regurgitation

Aortic regurgitation is the diastolic reversal of blood flow from the aorta into the left ventricle. The physical examination in these patients may reveal diagnostic clues: Quincke's pulse, an intermittent flushing of the nail beds that occurs when pressure is applied to the tip of the nail, which is synchronous with the heart rate.[4,22]

3. Infectious diseases

Infective endocarditis

Infective endocarditis (IE) results from the proliferation of microorganisms in the heart valves (both native and prosthetic), the ventricular septum and intracardiac devices. The characteristic lesion is the vegetation (a mass of fibrin, platelets, and microorganisms). Embolization of vegetation fragments results in distant infection and infarction via the deposition of immune complexes and bacterial antigens.[23] There are several skin manifestations of IE, and a complete dermatologic examination is mandatory.[24] Osler nodes are painful erythematous nodules on the pulp of fingers and toes, which disappear after a few days without sequelae. Janeway lesions are nontender, red macules on the palms and soles and tend to last longer. Though less specific, petechiae are the most common cutaneous sign of endocarditis, and they are seen on the conjunctivae, oral mucosa, and upper extremities.[2–4,25] A prospective observational analysis[24] found that patients with dermatologic manifestations had significantly more extracardiac complications, and cerebral complications in particular. The presence of skin lesions may suggest a state of active embolization and be a sign of IE severity.[24,25]

4. Inherited and/or congenital diseases

Marfan syndrome

Marfan syndrome (MFS) is an autosomal dominant (AD) connective tissue disease.[3,26] Its major clinical aspects are musculoskeletal, cardiovascular, cutaneous, and respiratory.[26,27] Patients with MFS are tall and thin, with scarce subcutaneous fat. They have a long and narrow face with crowded teeth, excessively long upper and lower extremities, long fingers (arachnodactyly), hyperextensible joints and altered body segments ratios such as arm span exceeding height. A sunken chest (*pectus excavatum*) or a protruding chest (*pectus carinatum*) are also common features. Other cutaneous manifestations include *striae distensae* located in the chest, shoulders, buttocks and thighs.[15] These patients may also have elastosis perforans serpiginosa (Fig. 3A): a rare skin disorder in which abnormal elastic tissue fibers pass from the dermis to the epidermis, presenting as a cluster of small papules in a serpiginous pattern.[2,4,26,27] Cardiovascular manifestations are the main cause of morbidity and mortality.[26,27]

Ehlers-Danlos syndromes

Ehlers-Danlos syndromes (EDS) (Figs. 3B and 3C) are a genetically heterogenous group of connective tissue inherited diseases that are characterized by joint hypermobility, anomalous skin texture and tissue fragility.[4,28] The clinical manifestations vary widely in severity depending on the disease subtype. Cutaneous findings include thin stretchable skin with visible subcutaneous vessels, atrophic and cigarette-paper scars, bruises and hyperpigmentation over the bony prominences and molluscum pseudotumors on the forearms. Cardiovascular manifestations include mitral valve prolapse, aortic root enlargement and bicuspid aortic valve.[2,4,28]

Cutis laxa

Cutis laxa is an elastin disorder [acquired or inherited (AD, recessive or X-linked)], in which skin loses its elasticity.[3,5] Clinical manifestations may be present at birth or develop during childhood. Children may appear prematurely aged and there are skin redundant folds hanging from the face and abdomen, with progressive looseness of the skin. These patients may have *cor pulmonale*, as well as aortic aneurysms and pulmonary artery stenosis.[3,29,30]

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is an inherited disease of the connective tissue that affects the cardiovascular system, the eyes and the skin, causing fragmentation and calcification of elastic fibers in the mid-dermis and calcification of small and medium size arteries.[3,4] The typical skin findings are waxy yellow papules that coalesce into plaques on elastic skin, affecting the flexure areas, especially the neck. The skin becomes inelastic and lax, looking like 'plucked chicken skin'.[3–5] Cardiovascular manifestations are common and include mitral valve prolapse and stenosis, CAD, PVD, cardiomyopathy and hypertension.[3–5] In addition, ophthalmologic findings are also hallmarks of the disease, including the development of angioid streaks and neovascularization in the retina followed by a retinal hemorrhage and scarring, with gradual loss of central and night vision and, ultimately, blindness.[31]

LEOPARD Syndrome

LEOPARD syndrome [lentigines, electrocardiographic (EKG) abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth and deafness][2–4] is an AD disease. Its cutaneous findings include multiple lentigines (Figs. 3D and 3E), mainly on the face, neck and upper trunk, sparing the lips and oral mucosa.[15] They are present in early childhood, and become darker and more abundant with age. A triangular-shaped face with frontal bossing, hypertelorism and low-set ears is typical. These patients may also have axillary ephelides,

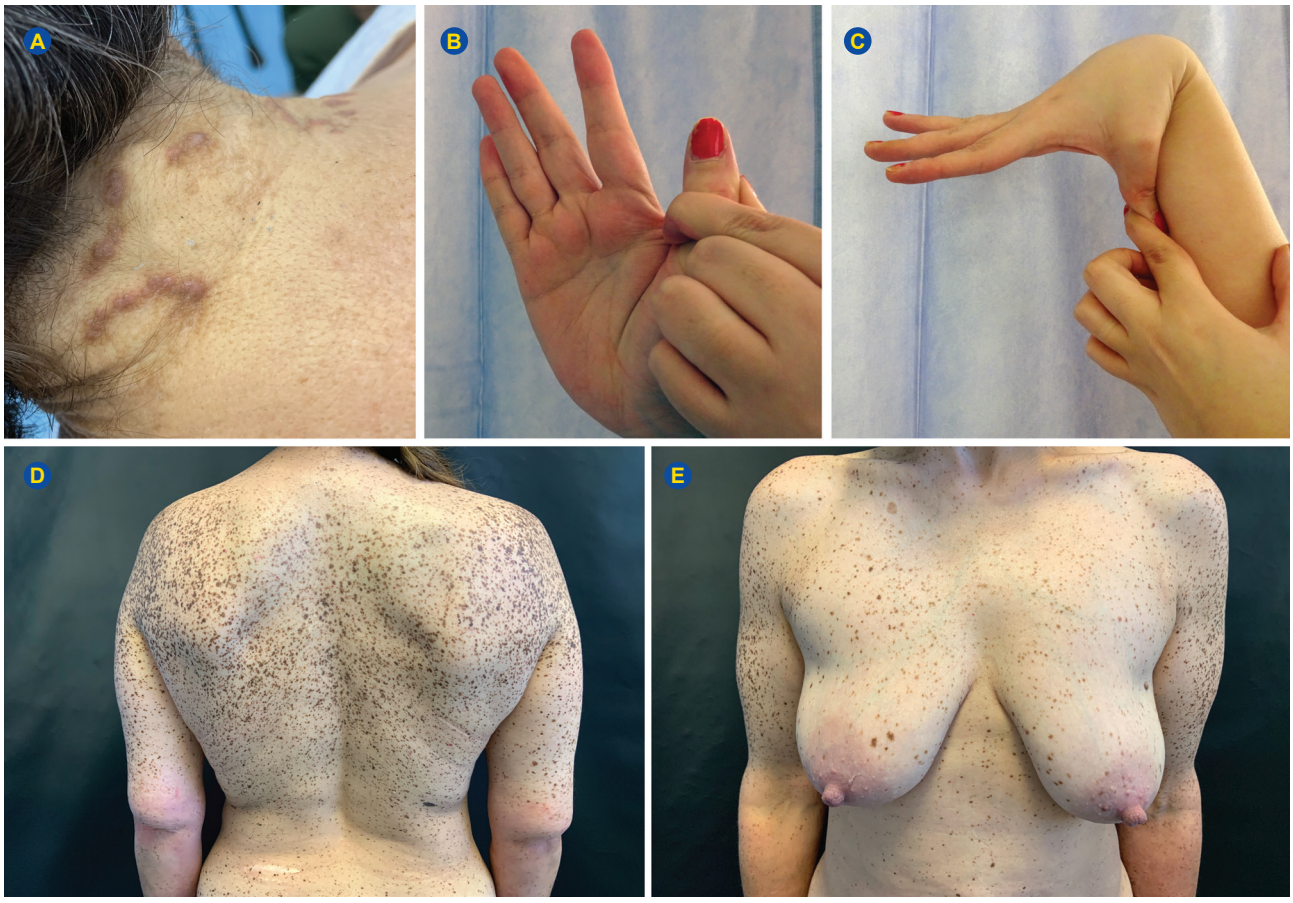

Figure 3 – (A) Elastosis perforans serpiginosa: a cluster of small papules grouped in a serpiginous pattern; (B and C) Ehlers-Danlos syndromes: joint hypermobility and hyperpigmentation over bony prominences of the hands; (D and E) LEOPARD syndrome: multiple lentigines on the upper trunk.

and café-au-lait spots.[2,3,32] The cardiovascular involvement in these patients is the major cause of morbidity and mortality and the most common heart defect is pulmonary valve stenosis.[3,4]

5. Vascular diseases

Chronic venous insufficiency

Patients with untreated chronic venous insufficiency may suffer from multiple sequelae including stasis dermatitis, lipodermatoslerosis, and venous ulcerations,[33,34] with a common mechanism – venous hypertension (from backward venous flow) leading to chronic inflammation.[33,35,36] Stasis dermatitis is a hallmark of venous disease, and its prevalence increases with age. Clinically, it appears as deficiently demarcated bilateral erythemato-squamous plaques on the lower limbs. Hyperpigmentation results from deposition of hemosiderin from the extravasated erythrocytes. Patients may have pruritus, cramps, restless legs and swelling.[33,35,37] With progressing disease, lipodermatosclerosis (fibrosis of the skin and subcutaneous tissue) may appear – the skin becomes rigid, indurated, fixed and shiny, contracting the subcutaneous tissue, which leads to shrinking of the lower leg volume, giving it an inverted bottle shape.[34] With gradual loss of epithelium, venous ulcers may arise.[33,34]

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by venous, arterial and microvascular thrombosis and obstetric complications in the presence of persistent antiphospholipid antibodies. APS is frequently associated with systemic lupus erythematosus (SLE) – secondary APS – but may also occur in the absence of other autoimmune diseases – primary APS.[38,39] Cutaneous manifestations may be the presenting feature of this disease. Livedo reticularis is the most frequent dermatologic finding of APS, usually widespread. Cutaneous necrosis and skin ulcers occur due to microvascular occlusion and appear as noninflammatory retiform purpura followed by a black necrotic plaque.[38–40]

MULTISYSTEMIC DISEASES THAT AFFECT THE HEART AND THE SKIN

1. Acute rheumatic fever

Acute rheumatic fever (ARF) is a postinfectious consequence of group A beta-hemolytic streptococcal pharyngitis.[3,41] ARF occurs because of an autoimmune response in which antibodies against streptococcal antigens cross-react to similar antigens in human tissues – molecular mimicry.[3,41,42] The clinical manifestations of ARF are summarized in the Jones criteria: fever, migratory arthritis, chorea, rash,

subcutaneous nodules and carditis.[3,41,43] The cutaneous manifestations of ARF include erythema marginatum and subcutaneous nodules, which are highly specific. Erythema marginatum is characterized by pink evanescent nonpruritic macules and papules involving the trunk and proximal extremities, which spread outwards into annular or polycyclic plaques in a centrifugal manner. As the lesions advance, the edges become raised and red and the center clears, becoming pale. Subcutaneous nodules are firm, painless protuberances seen on the extensor surfaces of the knees, elbows and wrists and are mostly seen in patients who have carditis.[3,41,43] Carditis is a major manifestation of ARF and may involve the endocardium, myocardium and pericardium – pancarditis. Valvulitis (causing mitral regurgitation) is the most consistent feature,[43] and is responsible for the cardiovascular morbidity and mortality in ARF.[3] The valvular damage may persist, resulting in chronic rheumatic heart disease.[41,43]

2. Syphilis

Syphilis is a sexually acquired infection caused by *Treponema pallidum*. It is characterized by a variety of clinical manifestations and involvement of multiple organ systems. If left untreated, chronic syphilis typically has intermittently active disease periods with primary, secondary, and tertiary stages as well as a latent (asymptomatic) period of variable length that occurs between primary and secondary stages (early) or before the onset of tertiary syphilis (late). Mucocutaneous manifestations vary widely. The primary stage of syphilis manifests as an indurated, painless, ulcerative chancre. Secondary syphilis occurs three to 12 weeks after the chancre and is characterized by a diffuse red-brown macular exanthema on the trunk and extremities (typically affecting palms and soles), associated with malaise, myalgia, low-grade fever and generalized lymphadenopathy. Tertiary syphilis is a systemic, multiorgan disease that occurs after a period of years or decades, including neurosyphilis (general paresis or tabes dorsalis), cardiovascular syphilis, or gummatous syphilis (a proliferative granulomatous process). Cutaneous manifestations of this late stage include noduloulcerative or gummatous lesions. Cardiovascular syphilis occurs 15 to 30 years after infection and may cause aortic aneurysms, aortic insufficiency, and myocarditis.[44,45]

3. Lupus erythematosus

Lupus erythematosus (LE) is an autoimmune disease with a variable clinical course.[46] LE may cause severe systemic organ involvement (SLE) or affect only the skin – cutaneous lupus erythematosus (CLE).[47] Cutaneous manifestations in SLE occur in 80% of patients and are the presenting feature in 25%.[4,5] CLE can be divided into acute, subacute and chronic forms, with decreasing probability of association with systemic disease.[47] Acute CLE is frequently associated with active SLE, it is sun-induced, transient and resolves without scarring – the malar butterfly erythematous rash is the characteristic feature. Subacute CLE (Fig. 4A) is characterized by arciform erythematous lesions involving the face, neck, upper trunk and shoulders. The most common form of chronic CLE is discoid lupus (Fig. 4B), which consists of erythematous scaly plaques with central atrophy and hypopigmentation, mainly on the head and neck.[47] Other nonspecific features of LE include splinter hemorrhages, red lunulae, oral ulcers, and alopecia.[2,4,47] Cardiac complications occur in half the patients with SLE and cause high morbidity and mortality. Pericarditis with pericardial effusion is the most common cardiac manifestation.[5,46,48]

4. Kawasaki disease

Kawasaki disease is an immune-mediated vasculitis of children under the age of five years. Although the etiology remains unknown, it is probably caused by an infectious trigger generating an abnormal immune response in genetically predisposed individuals. This disease may resolve without treatment, but serious cardiac sequelae may arise in the absence or delay of adequate treatment.[49,50] Diffuse maculopapular rash can occur within the first five days after the onset of fever. Extremity changes appear later – edema and erythema of the hands and feet, involving palms and soles, with ensuing desquamation beginning in periungual areas.[3] Kawasaki disease is one of the leading causes of acquired cardiac disease in children,[50] and coronary aneurysms are the most significant cardiac complication, developing in up to 25% of patients.[3,49]

5. Systemic sclerosis/scleroderma

Systemic sclerosis (SS) is an autoimmune disease characterized by widespread skin and internal organ fibrosis.[51] Cutaneous SS may be classified as limited or diffuse. Scleroderma is a prime feature of this disease. The limited form – symmetrical thickening of distal extremities and the face, with sclerodactyly, calcinosis cutis, and trophic ulcers – does not extend proximal to elbows and knees, or involve the trunk. Diffuse cutaneous SS is characterized by rapid symmetrical fibrosis of the distal and proximal extremities, with face and trunk involvement. Early skin findings on the hands include erythema, Raynaud's phenomenon and dilated nail-fold capillary loops. Typical facial features are shiny skin, loss of wrinkling, and puckering around the mouth. Cutaneous disease subtype has prognostic implications – in diffuse type, internal organ lesion is earlier and more severe.[2,4,51] Cardiovascular complications may arise with fibrotic visceral damage – fibrosis of the conduction system leads to arrhythmias and sudden death. Pulmonary hypertension with *cor pulmonale*, diastolic dysfunction, and HF may occur.[4,5,51]

6. Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unclear etiology. This disorders mostly involves the lungs (90% of patients) and the thoracic lymph nodes, presenting with lung infiltrates and bilateral hilar lymphadenopathy, but the skin and the cardiovascular system may also be involved.[5,52] Skin features are the most common

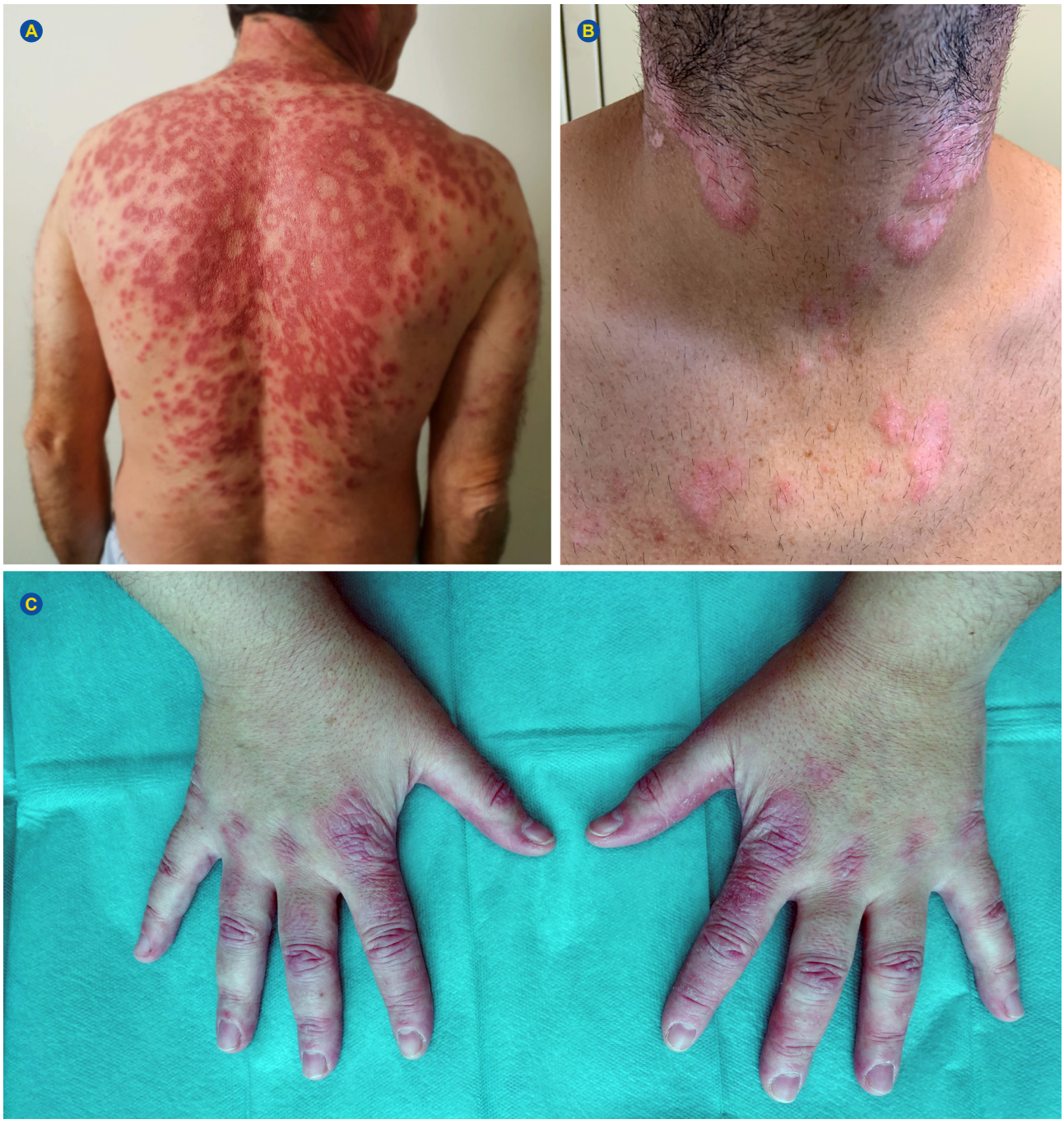

Figure 4 – (A) Cutaneous lupus erythematosus: subacute cutaneous lupus erythematosus (erythematous arciform plaques on the upper trunk and shoulders); (B) Cutaneous lupus erythematosus: chronic cutaneous lupus erythematosus (discoid lupus); (C) Dermatomyositis: Gottron's papules on the dorsal aspects of the hands.

extra-thoracic manifestations,[16] and are classified as specific or nonspecific, depending on whether non-caseating granulomas exist on skin biopsy. Erythema nodosum is the most frequent nonspecific and acute cutaneous feature. It is characterized by extremely tender subcutaneous erythematous nodules, mostly on the extensor surfaces of the limbs, often associated with fever and arthralgia. The most common specific lesions are symmetric granulomatous papules and plaques, mainly on the face, trunk, or extremities. Chronic sarcoidosis manifests with lupus pernio (indurated bluish plaques on the nose).[52,53] Cardiac involvement (cardiomyopathy, conduction disturbances and ventricular arrhythmias) may be occult, but is associated with poor prognosis.[52]

7. Dermatomyositis

Dermatomyositis (DM) is an idiopathic myopathy, characterized by distinct skin lesions and clinically heterogeneous systemic manifestations. Cutaneous manifestations can be divided into pathognomonic, characteristic,

compatible, less common, rare and non-specific. Pathognomonic manifestations include: Gottron's papules (violaceous plaques overlying the metacarpophalangeal and proximal interphalangeal joints of the hands) (Fig. 4C), Gottron's sign (erythematous plaques over the extensor surfaces of elbows and knees) and heliotrope rash (periorbital erythema with edema). Characteristic skin features include nail-fold changes (periungual erythema and telangiectasias), shawl sign (violaceous plaques on the neck, shoulders and upper back), V sign (erythematous plaques on the lower anterior neck and upper back), and Holster sign (symmetric poikiloderma – hypo- or hyperpigmentation, telangiectasia, and atrophy (reticulated, livedoid or linear) – on the hips and lateral thighs). Other less frequent skin changes are vesiculobullous or ulcerative lesions, cutaneous vasculitis, calcinosis cutis, mechanic's hands (hyperkeratosis and fissuring of fingers and palms), deck-chair sign (erythematous eruption sparing transverse skin folds), and Raynaud's phenomenon. The clinical course of skin lesions does not necessarily parallel that of muscle disease and may precede or follow myositis. Cardiac involvement may develop at any time, with subclinical diastolic dysfunction, myocarditis, myocardial fibrosis, arrhythmias, and HF.[54,55]

DERMATOLOGIC MANIFESTATIONS OF CARDIOVASCULAR THERAPEUTICS

1. Bypass surgery

Patients who undergo bypass surgery are at risk of developing various cutaneous abnormalities. The great saphenous vein is usually used as conduit in coronary revascularization. Vein graft dermatitis may occur months after bypass surgery: a reddish-brown, scaly, fissured dermatitis along the distal portion of well-healed saphenous vein graft scar.[3,5,56]

2. Drugs

Many cardiovascular therapeutic drugs may have cutaneous adverse effects. Angiotensin-converting enzyme inhibitors may cause angioedema. Heparin-induced skin necrosis may occur as a result of hypersensitivity angiitis. Patients with long term use of amiodarone can sometimes develop blue dermal melanosis of the face, mainly in sun-exposed areas. A lupus-like syndrome may occur during treatment with amiodarone, procainamide and hydralazine. Beta-blockers and calcium channel blockers may exacerbate psoriasis or cause new psoriasiform eruptions. Calcium channel blockers such as amlodipine may cause bilateral malleolar edema due to their vasodilatory effect. Thiazide diuretics are classified as sulfonamides and they can produce several types of eruptions in patients previously sensitized to other sulfonamide drugs.[2,57–59]

AUTHOR CONTRIBUTIONS

CB: Conception of the work, draft of the manuscript, literature review.

RP, CQ: Literature review, critical review of the manuscript.

PF, LMF: Conception of the work, literature review, critical review of the manuscript.

PATIENT CONSENT

Obtained.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Serratia marcescens Endocarditis: A Case Report and Literature Review

Endocardite por *Serratia marcescens*: Caso Clínico e Revisão da Literatura

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ABSTRACT

Serratia marcescens is a rarely implicated agent in endocarditis. We describe a case of a patient that underwent aortic and mitral valve replacement for *Streptococcus agalactiae* endocarditis. Four months later, he was readmitted with an ischemic stroke and fever. Physical examination and repetitive transthoracic echocardiogram were unremarkable. The initial blood cultures were negative. Due to sustained fever, vancomycin, gentamicin and piperacillin-tazobactam were initiated. On subsequent blood cultures, *Serratia marcescens* was isolated and antibiotics switched to ertapenem and gentamicin. In addition to cerebral emboli, a splenic embolus was found. The PET/CT revealed an abnormal hypercaptation in the mitral bioprosthesis. The patient was treated for six weeks. There are no current specific recommendations regarding the treatment of *Serratia marcescens* endocarditis. It is widely accepted that treatment should be prolonged and include a combination of antimicrobial agents. Morbidity and mortality are high, particularly when there's the need for surgical replacement. In this case, however, the patient ended-up only requiring medical treatment due to the favourable response.
Keywords: Endocarditis, Bacterial; Fever; Heart Valve Prosthesis; Positron-Emission Tomography; Serratia marcescens

RESUMO

A *Serratia marcescens* é um agente raro de endocardite. Descrevemos o caso de um doente submetido a substituição das válvulas aórtica e mitral por endocardite causada por *Streptococcus agalactiae*. Quatro meses após, é readmitido por evento cerebral isquémico e febre. Ao exame objetivo não evidenciava alterações e os ecocardiogramas transtorácicos eram normais. As hemoculturas colhidas à admissão foram estéreis. O doente manteve-se febril, iniciando-se empiricamente vancomicina, gentamicina e piperacilina-tazobactam. Após isolamento de *Serratia marcescens* em hemoculturas subsequentes, a antibioterapia foi ajustada para ertapenem e gentamicina. Para além de um êmbolo cerebral, foi encontrada embolia esplénica e hipercaptação anormal na prótese mitral biológica em PET. Foi efetuado tratamento durante seis semanas. Não existem recomendações específicas sobre o tratamento de endocardite por *Serratia marcescens*, mas deve ser prolongado e com terapêutica combinada. A morbimortalidade é elevada, sobretudo quando há necessidade de cirurgia. Neste caso, a evolução clínica favorável do doente permitiu o tratamento médico exclusivo.
Palavras-chave: Endocardite Bacteriana; Febre; Próteses Valvulares Cardíacas; Serratia marcescens; Tomografia por Emissão de Positrões

INTRODUCTION

Serratia marcescens is a facultative anaerobic, Gram-negative bacillus, mostly associated with intravenous drug users (IVDU) and hospital-acquired infections.[1] *Serratia marcescens* endocarditis is extremely rare (0.14% of all cases in a prospective cohort).[1] In non-IVDU patients, it can be associated with immunosuppression, chronic disease, indwelling catheterization and presence of cardiac devices/prosthetic valves.[2]

We describe a case of healthcare-associated endocarditis caused by *Serratia marcescens*.

CASE REPORT

A 61-year-old man, smoker, with severe aortic stenosis, was admitted to hospital due to acute pulmonary oedema. He was diagnosed with mitral endocarditis caused by *Streptococcus agalactiae*. He received treatment with gentamicin 5 mg/kg/day for two weeks and ceftriaxone 2 g/day. After four weeks, he underwent mitral valve replacement with a bioprosthesis due to valvular insufficiency and aortic valve replacement. He had sterile valve and control blood cultures (BC), hence completing two more weeks of antibiotics. Two months later, he was diagnosed with non-small cell lung cancer stage IIB and a transthoracic echocardiogram detected a filiform structure in the mitral bioprosthesis and a thrombus in the left atrial posterior wall, for which he was hypocoagulated with warfarin.

Two months later, the patient presented to the emergency department with left homonymous hemianopia and fever. He had a temperature of 38.3ºC, the remaining physical examination was unremarkable. The electrocardiogram showed sinus rhythm. The blood tests showed normal leukocyte count and C-reactive protein (CRP) level of 51 mg/L [< 3.0 mg/L]. A brain computerized-tomography (CT) revealed an ischemic lesion in the left parietal-occipital region and smaller lesions in the left and right parietal regions (Fig. 1). Upon admission, a transesophageal echocardiogram

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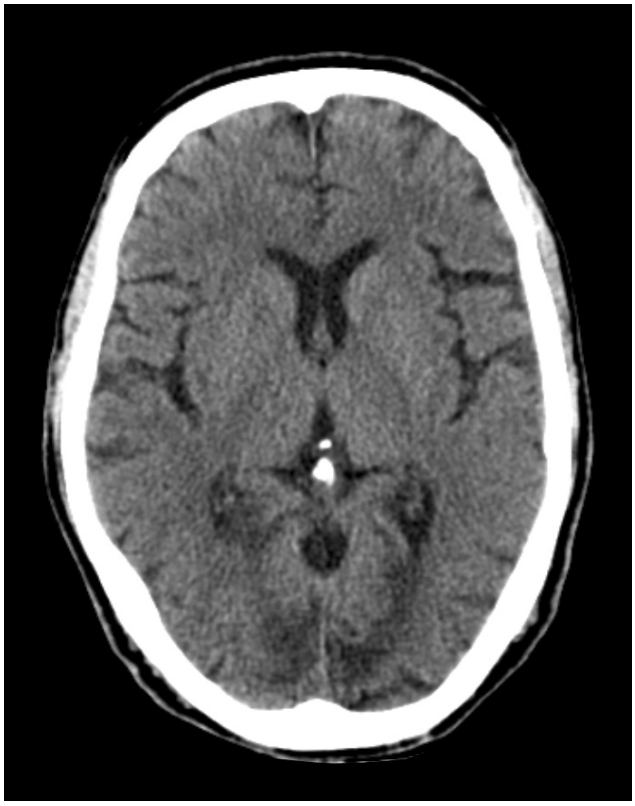

Figure 1 – Brain-CT showing ischemic lesion in the left parietal-occipital region

(TEE) documented a smaller thrombus and absence of valvular vegetations, abscess or ventricular dysfunction. A cardiac-CT did not display signs of inflammation and corroborated these findings. Three sets of BC were negative. The patient remained apyrexial and, in the presence of lung cancer as a possible aetiology, antibiotics were not started.

On the ninth day, the patient had recrudescence of fever and shivering. Blood pressure was 68/43 mmHg, pulse 105 bpm, temperature 39.6ºC and he became disoriented. Neither new extra cardiac sounds or murmurs nor cutaneous changes were noticed. Laboratory data revealed a lactate level of 6.45 mmol/L [< 2.0 mmol/L], increased leukocyte count and CRP (138.9 mg/L). A chest radiography did not show any changes. The blood pressure responded to fluid resuscitation. He received empirical treatment with vancomycin 25 mg/kg/dose and gentamicin 5 mg/kg/day for possible endocarditis and piperacillin-tazobactam 4.5 g each tid for possible nosocomial infection. Two days later, *Serratia marcescens*, without antimicrobial resistance *in vitro*, was isolated in three sets of BC, while urine culture was sterile. Gentamicin was maintained, but the remaining antibiotics were switched to ertapenem 1 g/day. A thoracic-abdominal-pelvic-CT scan revealed a splenic infarct (Fig. 2). Repeated TEE showed overlapping results. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron-emission-tomography (PET-CT) showed an abnormal hypercaptation in the inferior part of the mitral valve.

Because the patient had one major criterion (abnormal activity around the prosthetic valve) and four minor criteria (predisposing heart condition, fever, septic emboli and positive BC), the diagnosis of *Serratia marcescens* endocarditis was established, according to the modified European Society of Cardiology criteria. The patient's favourable clinical evolution and subsequent sterile BC two days after commencing treatment allowed completion of the antibiotic scheme (gentamicin for two weeks due to acute kidney injury and ertapenem for six weeks),and enabled the administration of ertapenem in the outpatient clinic.

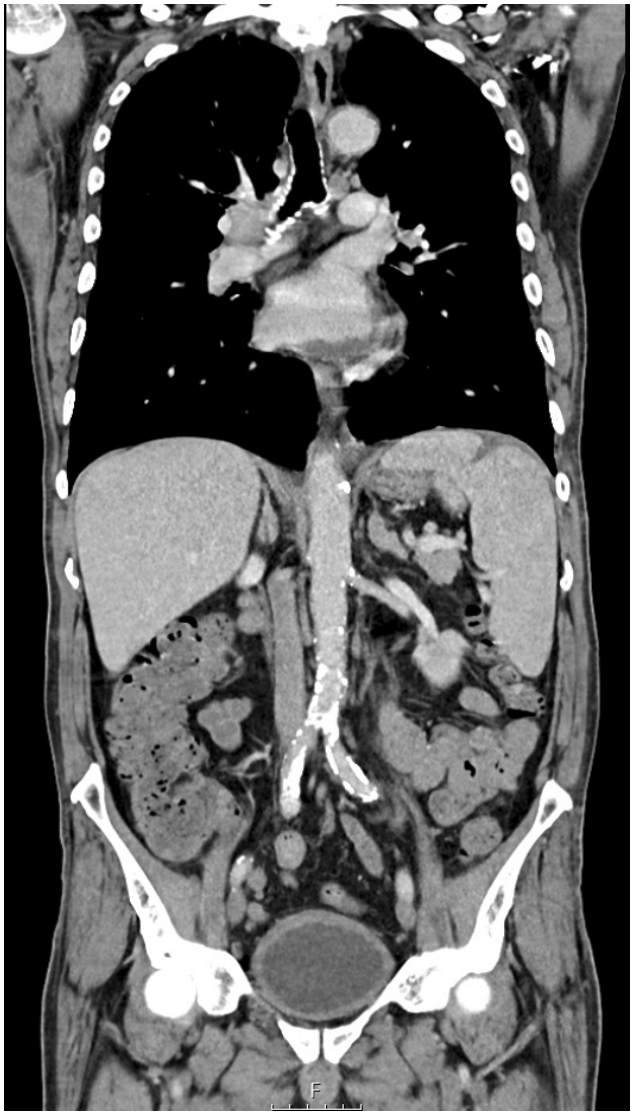

Figure 2 – Abdominal-CT scan revealing an enlarged spleen and an area of infarct in its superior lobe

DISCUSSION

Serratia marcescens endocarditis was first described in 1951.[1] Only 15 cases were reported since 1994 (Table 1).[1-15] In nine cases, the risk factor for infection was IVDU; in the group of health-care-associated endocarditis only one had a prosthetic valve[8] and one pacemaker.[5] Similarly, most of the cases had either immunosuppressive or chronic disease. All patients had positive blood cultures. Three patients died due to systemic and cerebral embolisation; seven patients underwent surgery for foci control. Additionally, this

Table 1 – Published cases of *Serratia marcescens* endocarditis since 1994

Reference	Age / gender	Risk factor	Medical history	Location	Evolution	Treatment	Outcome
J Infect 1994[3]	50yo, female	Health-care associated	Non-Hodgkin lymphoma, central venous catheter	Native AV	Septic emboli to skin	ATB: azlocillin + gentamicin, six weeks	Clinical resolution
Lancet Infect Dis 2007[4]	43yo, female	Not known	Splenectomy	Native MV	CNS embolisation and abscess formation	ATB: cefepime six weeks + gentamicin two weeks	Clinical resolution
BMJ Case Rep 2009[5]	67yo, male	Health-care associated	Pacemaker	Pacing wire	No complication	ATB: meropenem + gentamicin, then ciprofloxacin two weeks + pacemaker explantation	Clinical resolution
Intern Med 2012[6]	85yo, female	Health-care associated	Diabetes mellitus, Hypertension	Native MV	CNS embolisation: multiple infarctions Heart failure	ATB: ceftazidime six weeks + gentamicin one week	Death
J Echocardiogr 2012[7]	82yo, male	Health-care associated	Cirrhosis	Native TV, right ventricle	No complication	ATB: cefmetazole + clindamycin (duration not specified)	Clinical resolution
Scott Med J 2013[8]	65yo, female	Health-care associated	Post-Bentall procedure	Prosthetic AV	Bilateral endogenous endophthalmitis	ATB systemic: meropenem + gentamicin + ciprofloxacin (duration not specified) + local: ceftazidime	Clinical resolution
Infect Dis Clin Pract 2016[1]	46yo, male	IVDU	HIV, HCV, IVDU	Native MV	CNS embolisation: multiple infarctions and haemorrhage	ATB; meropenem (duration not specified)	Death
J Investig Med High Impact Case Rep 2018[9]	42yo, male	IVDU	HCV, IVDU	Native PV	Pulmonary embolism	ATB: ceftriaxone six weeks + valve replacement	Clinical resolution
Case Rep Infect Dis 2018[2]	53yo, male	IVDU	HCV; IVDU, coronary artery disease	Native AV	Multiple site embolisation: CNS, abdomen, testicle, vertebral body	ATB: ertapenem + ciprofloxacin six weeks + valve replacement	Clinical resolution
Case Rep Infect Dis 2019[10]	41yo, male	Health-care associated	Recent knee joint arthrocentesis	Native MV	Localised alveolar haemorrhage	ATB: gentamicin two weeks + meropenem + ciprofloxacin six weeks	Clinical resolution
Aorta 2020[11]	24yo, male	IVDU	Bicuspid AV, chronic Stanford's type-B aortic dissection, IVDU	Native AV	AV root abscess Embolisation: spleen, kidneys	ATB (not stated) + valve replacement	Clinical resolution
IDCases 2020[12]	55yo, male	IVDU	IVDU	Native AV, left ventricle	Embolisation: spleen, kidneys	ATB: cefepime + levofloxacin (duration not specified)	Death
Case Rep Infect Dis 2020[13]	33yo, male	IVDU	Hodgkin lymphoma, AV stenosis, HCV, IVDU	Native AV	Complete AVB, possible AV root abscess	ATB: cefepime six weeks + ciprofloxacin four weeks	Clinical resolution
Heart Lung Circ 2020[14]	50yo, male	IVDU	IVDU	Native AV	AV root abscess, complete AVB, Heart failure	ATB: meropenem + ciprofloxacin 6 weeks + valve replacement + pacemaker implantation	Clinical resolution
Cureus 2020[15]	27yo, female	IVDU	HCV, IVDU	Native TV	Pulmonary septic emboli Blood cultures: *Serratia marcescens* + MSSA	ATB meropenem six weeks (not stated ATB for MSSA) + percutaneous aspiration of emboli	Clinical resolution

These were case reports included in PubMed about *Serratia marcescens* endocarditis, but only the last case in the table reported the isolation of two microorganisms in blood cultures (*Serratia marcescens* and *Staphylococcus aureus* methicillin-susceptible). ATB: antibiotics, AV: aortic valve; AVB: atrioventricular block; CNS: central nervous system; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IVDU: intravenous drug use; MSSA: methicillin-susceptible *Staphylococcus aureus;* MV: mitral valve; PV: pulmonic valve; TV: tricuspid valve

microorganism has an unexplained trend for left-sided valvular involvement[1] with a 68% mortality rate.[12] Right-sided endocarditis was described in three cases: two were IVDU and one had percutaneous transhepatic portal embolization.[7]

In the absence of a clinically evident infection, persistent fever and mild elevation of inflammatory parameters, in a patient with prosthetic cardiac valve, should trigger the suspicion of endocarditis, leading to an exhaustive investigation. In these cases, a negative TEE does not rule out the diagnosis and additional imaging should be performed, particularly PET-CT. The abnormal uptake of FDG in inflammatory tissue around the valve is highlighted in the PET-CT with a sensitivity of 70% - 100%,[1] which increases the likelihood of a positive diagnosis.

After the definitive diagnosis, the choice of antimicrobial therapy posed another challenge as there are no current specific guidelines concerning this issue and existing data comes from case reports. Nevertheless, it is widely accepted that treatment should be prolonged, and that dual antimicrobial therapy should include synergic and bactericidal agents. The suggested treatment is a combination of a beta-lactam and an aminoglycoside for at least six weeks.[2] Another challenge posed by *Serratia marcescens* infections is the presence of strains resistant to multiple antibiotics, namely penicillins, first-, second- and third-generation cephalosporins and, in some cases, carbapenems.[1] These resistances may be induced by prior use of beta-lactams, which may be the reason why a carbapenem is a stronger option in many cases of *Serratia* bacteremia. Therefore, we opted to use carbapenem due to is favourable experience in the literature, with a higher number of successful cases compared with other antibiotics. Resistance is mainly mediated by production of chromosomal AmpC cephalosporinases and synthesis of beta-lactamases, including extended spectrum beta-lactamases and carbapenemases.[1,10] Concurrent administration of aminoglycosides leads to a rapid sterilization of the affected valve.[1]

In most patients, antimicrobial therapy is insufficient and surgical treatment is needed due to poor prognosis[13] and the pathogenicity of the microorganism.[1] This may be recommended within the first seven to 10 days after beginning antimicrobial therapy.[13] In contrast with the majority of cases described, surgery was deemed unnecessary in our patient as he remained asymptomatic with normal valve function after receiving antibiotic therapy. Despite the presence of a prosthetic valve, the causative agent, the patient's comorbidities and the occurrence of cerebral septic emboli, our case may be an example that, in some selected patients and according to clinical evolution, antibiotic treatment may be sufficient.

This case highlights the importance of early identification and diagnosis in order for appropriate treatment to be initiated despite the lack of specific guidelines about this subject.

AUTHOR CONTRIBUTIONS

AIF: Follow up of the patient, literature research, draft of the manuscript.

FOS, JR, MH: Follow up of the patient, literature research, critical review of the manuscript.

JA: Follow up of the patient, final approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Campylobacter jejuni Pericarditis: A Case Report

Pericardite por *Campylobacter jejuni*: Um Caso Clínico

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ABSTRACT

Campylobacter jejuni is one of the most common causes of enteritis. In rare cases, extraintestinal infection can occur, with a handful of cases of cardiac involvement, of which the pathophysiological mechanism is unclear. We report a case of pericarditis in a patient with X-linked agammaglobulinemia presenting with chronic diarrhea and chest pain who evolved to cardiac tamponade, requiring a pericardial window and a long course of broad-spectrum antibiotics. To the best of our knowledge, this is the third case of pericarditis caused by *Campylobacter jejuni* reported in the literature, the second in a patient with X-linked agammaglobulinemia. Despite its rarity, this case serves as a reminder of *Campylobacter* as a potential cause of cardiac inflammation for clinicians treating pericarditis/myocarditis, especially in patients with a history of diarrhea or immunosuppression.
Keywords: Agammaglobulinemia; Campylobacter Infections; Campylobacter jejuni; Pericarditis

RESUMO

A *Campylobacter jejuni* é uma das causas mais comuns de enterite. A infeção extraintestinal pode ocorrer raramente, estando reportados alguns casos de atingimento cardíaco, de mecanismo fisiopatológico incerto. Reportamos um caso de pericardite num doente com agamaglobulinemia ligada ao X, que se apresentou como diarreia crónica e dor torácica, evoluindo para tamponamento cardíaco com necessidade de confeção de janela pericárdica e tratamento prolongado com antibióticos de largo espectro. Este é, tanto quanto é do nosso conhecimento, o terceiro caso de pericardite por *Campylobacter jejuni* reportado na literatura, o segundo em doente com agamaglobulinemia ligada ao X. Apesar da sua raridade, este caso serve para reforçar a importância do género *Campylobacter* como causa de inflamação cardíaca para médicos que tratem pericardite/miocardite, especialmente em doentes com história de diarreia ou imunossupressão.
Palavras-chave: Agamaglobulinemia; Campylobacter jejuni; Infecções por Campylobacter; Pericardite

INTRODUCTION

Campylobacter spp. are one of the most common pathogens associated with human enteritis, and represent a zoonosis with a worldwide distribution.[1] Two species account for the majority of infections, with *Campylobacter jejuni* (*C. jejuni*) being the prototype for intestinal infection and *C. fetus* more associated with extraintestinal manifestations, usually as an opportunistic infection. These can be protean, with well documented descriptions of persistent bacteremia, cholangitis/cholecystitis, central nervous system infection, septic arthritis, osteomyelitis, septic abortion, mycotic aneurysms, endocarditis and myopericarditis.[1] The diagnosis requires a high degree of clinical suspicion, due to the relative rarity of these manifestations and frequently absent gastrointestinal symptoms. Compounding this extensive spectrum of clinical expressions, antimicrobial resistance is a growing problem especially in developing countries, with a significant number of isolates being resistant to macrolides and quinolones in particular.[2,3]

Furthermore, *C. jejuni* has been associated with several immunological sequelae, such as reactive arthritis, Guillain-Barré syndrome, hemolytic-uremic syndrome and small intestinal MALT (mucosal associated lymphoid tissue) lymphoma.[1]

CASE REPORT

A 34-year-old male with a history of X-linked agammaglobulinemia treated with monthly subcutaneous immunoglobulin and bronchiectasis presented to the emergency department with a seven-month history of non-bloody diarrhea and intermittent fever, chest pain and orthopnea.

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There was a history of consumption of undercooked poultry and several cases of diarrhea several months before in his area of residence. There was no recent travel history. He had received two courses of antibiotics (amoxicillin/clavulanate) and had two negative stool cultures (collected on two occasions, namely four months and one month prior to hospital admission). On physical examination there was fever, tachycardia, hypotension, medium volume ascites and hepatomegaly. There was hyperlactatemia, elevation of markers of systemic inflammation and cholestasis, with normal hepatic and renal function. A chest radiography showed an enlarged bottle-shaped heart and echocardiography showed a large volume pericardial effusion. The electrocardiogram and cardiac enzymes were normal.

Upon intravenous hydration he developed signs of pulmonary edema, with serial echocardiography showing signs of imminent tamponade with right ventricle dysfunction, requiring pericardiocentesis on the first and second day and window pericardiectomy on the third day. The analysis of the pericardial fluid and biopsy revealed pyogenic inflammation (86 585/µL leukocytes, 79 577/µL neutrophiles and 7008/µL mononucleated cells) with elevated ADA (adenine deaminase), with a negative Gram examination and culture, no granulomas and a negative flow cytometry for lymphoma.

Due to the insidious clinical presentation, he was empirically treated for pericardial tuberculosis with systemic glucocorticoid therapy and an alternative drug regimen due to significant hepatic cholestasis, comprising ethambutol, levofloxacin and amikacin for 10 days. This course of treatment was abandoned after all the biologic samples (four sputum, three pericardial fluid samples and the pericardial biopsy sample) were negative for granulomata, alcohol-acid resistant bacilli and *Mycobacterium tuberculosis* by polymerase chain reaction.

Ten days after hospital admission, the blood cultures became positive for *C. jejuni*, and the diagnosis of invasive campylobacteriosis was made. The patient was thus started on imipenem and an antibiotic susceptibility test later confirmed susceptibility to carbapenems and aminoglycosides and resistance to quinolones, macrolides, beta-lactam/beta-lactamase inhibitor and tetracyclines.

After six weeks of treatment there was complete recovery, with echocardiography showing no residual effusion and normal systolic function of both ventricles.

DISCUSSION

Campylobacter species are commensal microorganisms in the digestive tract of several species, including fowl, dogs, swine, sheep and cattle. Human infection by *C. jejuni* starts one to seven days after consumption of contaminated meat, milk or water, leading to a febrile illness followed by non-characteristic diarrhea and abdominal pain, usually resolving in one week even without antibiotic treatment.[1,4] Portal and even systemic bacteremia seem to be a common occurrence, with spontaneous clearance in the immunocompetent host. In patients with immunoglobulin deficits, this species has been documented to cause chronic infection.[5] Due to the presence of a proteinaceous capsule that protects it from the opsonizing (coating by the C3b fragment of complement that signals for phagocytosis by macrophages) and lytic effects of complement, *C. fetus* has a much greater tendency to evade the immune system, resulting in a more protracted clinical course, persistent bacteremia and seeding of distant organs.[6]

Several cases of cardiac involvement have been described (pericarditis, myopericarditis and myocarditis), by both *C. fetus* and *C. jejuni* but while the former has almost always been isolated from blood or pericardial fluid samples, it is seldom the case with the latter.[7–10] This has led some scientists to question whether the pathophysiological mechanism behind cardiac inflammation could differ between both species, with *C. fetus* being related with direct bacterial/bacterial toxin mediated damage and *C. jejuni* resulting from a type 2 hypersensitivity reaction to bacterial antigens.[7] The latter has been supported by the well-documented role played by this species in the development of reactive arthritis and Guillain-Barré syndrome. However, our case may disprove this hypothesis: on the one hand, *C. jejuni* was isolated from blood cultures, indicating at least a potential for direct cardiac invasion even if not identified in pericardial fluid cultures (bearing in mind that these were obtained when the patient was already being treated with an aminoglycoside); on the other hand, the coexistence of X-linked agammaglobulinemia might be 'protective' against immune pericarditis by a type 2 hypersensitivity reaction, since the production of antibodies is severely decreased. However, this does not exclude other immune mechanisms, such as T-cell mediated tissue damage. To the best of our knowledge there are only two other cases of exclusive pericardial involvement by *C. jejuni* reported in the literature,[11,12] one of them in a patient suffering from X-linked agammaglobulinemia,[12] akin to our patient.

Our case serves as a highlight to remind clinicians treating patients with pericarditis or myocarditis of the possibility of infection by *Campylobacter*. This may be especially important when gastrointestinal symptoms or immunosuppression coexist, with the diagnosis being made by non-invasive tests such as blood and stool cultures or even serology, where available. As this case underscores, a negative stool culture does not exclude the diagnosis, and when possible, several samples plus blood cultures should be taken. Awareness of this manifestation of *Campylobacter* infection may avoid unnecessary invasive procedures, such as coronary catheterization, and improve outcomes by prompt treatment with antimicrobials which must be adapted to local antibiotic susceptibility.

AUTHOR CONTRIBUTIONS

JNM: Literature review, draft of the manuscript.
CG, AM, RA: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical

Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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"Trapped" Lung from Calcified Fibrothorax

Pulmão "Encarcerado" por um Fibrotórax Calcificado

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Keywords: Fibrosis; Lung; Thoracic Diseases
Palavras-chave: Fibrose; Doenças Torácicas; Pulmão

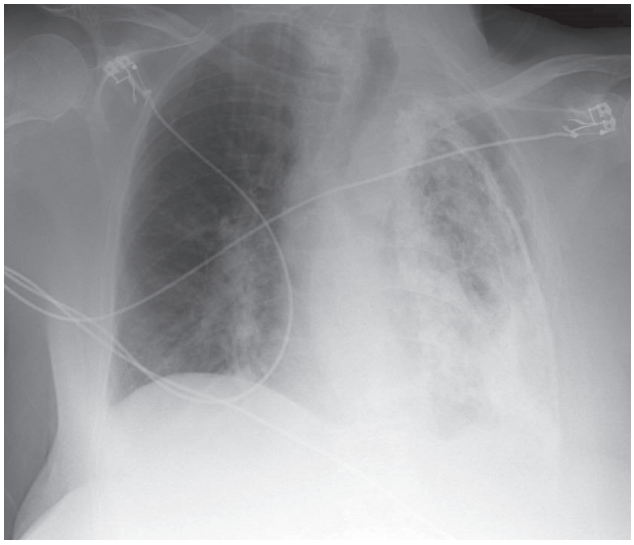

Figure 1 – Chest radiograph shows nearly complete left pleural calcification and marked lung volume reduction

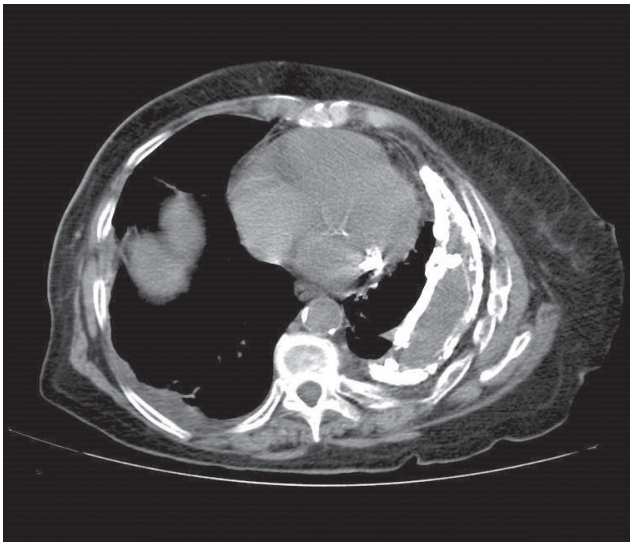

Figure 2 – Computerized tomography with extensive calcification of left lung fibrothorax

A 91-year-old woman presented with a 2-week history of dyspnea and productive cough. She was autonomous regarding the activities of daily living and had a medical history of type 2 diabetes, hypertension and suspected tuberculosis in her twenties. The arterial blood gas test revealed severe hypercapnia with acidemia. The chest radiograph (Fig. 1) showed a nearly complete left pleural calcification associated with a marked lung volume reduction and computerized tomography (Fig. 2) confirmed a calcified fibrothorax.[1] A thick 'peel' formed on both pleural surfaces, preventing complete lung expansion, and thus limiting functional reserve.[2] These exuberant findings are unusual but strongly suggestive of late sequelae from untreated pleural tuberculosis. A respiratory infection led to multifactorial respiratory failure associated with the pleural disease, age-related chest wall weakness and pulmonary congestion. The patient was successfully managed with conservative treatment. These findings portray the clinical and physiological implications of a trapped lung.

AUTHOR CONTRIBUTIONS

MB: Conception and coordination of the work; draft of the manuscript.

MT, RM: Critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

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Medico-Legal Examination of Sexual Assaulted Victims Unable to Consent in Portugal: Ethical Decision-Making

Exame Médico-Legal de Vítimas de Agressão Sexual Incapazes de Consentir, em Portugal: Tomada de Decisão Ética

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ABSTRACT

Medical decision-making is a complex task in any field. In the medico-legal examination of victims that have (allegedly) been sexually assaulted there are many specific variables and features influencing the decision. It is essential to complement the clinical intervention with a forensic approach. Clinical parameters such as the victim's physical and cognitive state along with circumstantial information such as the elapsed time from the event and the type of abuse (described or suspected) grant different levels of priority to the forensic medical assessment. In such cases, forensic medical doctors or other medical doctors responsible for attending to the victim may have to decide whether to perform the examination prior to a judicial analysis of the case if consent cannot be obtained. This implies the need to deliberate about performing the examination and/or reporting the case to legal authorities. This article discusses the forensic medical decision-making process in cases of alleged recent sexual assault of victims who are legally unable to consent or unable to consent for other reasons. We aimed to identify possible ethical problems that can arise in this context and discuss which elements should be considered by medical doctors when making decisions about such cases. The Portuguese legal framework of medico-legal examinations is analyzed. The authors also make considerations about reporting these cases from a legal point of view. The discussion turns to an ethical perspective where possible ethical problems arising from medical deliberation are identified. Issues about legally incompetent victims and incompetent victims due to other reasons are addressed. A decision-making tree, based on the problems identified, is proposed.

Keywords: Child Abuse, Sexual; Crime Victims/legislation & jurisprudence; Forensic Medicine; Informed Consent; Mandatory Reporting

RESUMO

A deliberação médica é uma tarefa complexa. Na área médico-legal, em contexto de avaliação de alegadas vítimas de crime sexual, existem muitas especificidades que influenciam a deliberação. Nestes casos é essencial complementar a intervenção clínica com a abordagem forense. Parâmetros clínicos tais como o estado físico e cognitivo em conjugação com a informação circunstancial, nomeadamente o período de tempo decorrido desde o evento em apreço e o tipo de prática sexual suspeitada, conferem diferentes níveis de urgência à realização da perícia médica. Em certos casos pode justificar-se que o médico forense ou outro que preste assistência à vítima avance com o a perícia médica previamente à existência de uma ordem judicial. Tal implica que a deliberação deverá contemplar a tomada de decisão sobre a realização da perícia, mas também sobre o dever de denúncia às autoridades judiciais. Neste artigo, os autores discutem o processo de deliberação ética nos casos de alegações de crime sexual cometido recentemente, quando a vítima se encontra em situação de incapacidade para consentir no momento da realização da perícia. O objetivo é identificar os problemas éticos subjacentes e determinar que elementos deverão ser considerados pelos médicos para deliberar neste contexto. Com esse foco os autores fazem uma análise do enquadramento legal das perícias médicas em Portugal. Numa segunda fase identificam e discutem os problemas éticos em relação com este tipo de casos. São abordadas questões relacionadas com vítimas incapazes de consentir. Conjugando os elementos resultantes das primeiras fases do trabalho é, por fim, apresentada uma árvore de decisão passível de ser usada no processo de deliberação neste tipo de casos.

Palavras-chave: Abuso Sexual de Criança; Consentimento Informado; Denúncia de Crime; Medicina Forense; Vítimas de Crime/legislação e jurisprudência

INTRODUCTION

In Portugal, forensic and medico-legal examinations of (allegedly) sexually assaulted victims are a competency of the National Institute of Legal Medicine[1] and are usually performed following orders from legal authorities. However, clinical parameters such as the victim's physical and cognitive state along with circumstantial information such as the elapsed time from the event and the type of described or suspected abuse grant different degrees of urgency to forensic medical assessment. The Portuguese law, which has a code-driven 'civil law' legal framework, as do other countries of mainland Europe, establishes that if a forensic medical examination is particularly urgent[2] it should be carried out as soon as possible in order to collect traces or samples that may be lost or modified rapidly over time. Therefore, forensic medicine physicians or other medical doctors responsible for attending to the victim may have to decide whether to perform the examination prior to a judicial analysis of the case if informed consent cannot be obtained.[2,3] That can be the case when recent non-consensual sexual activity between the victim and the offender is suspected.

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Moreover, the examinee is expected to be in a state of particular vulnerability, not only because (s)he is an alleged victim of a crime but also because (s)he may foresee the future legal investigation as disruptive and stressful. From a clinical point of view, medical assessment implies a physically invasive examination or procedure(s) to document bodily harm and preserve evidence. It is relevant to respect the victim's will and rights, but medical doctors cannot overlook their social, deontological and legal duties when deciding whether to report the case and help the justice system (in any possible way). But any negative consequences of reporting false allegations are not any less serious than those of failing to report actual abuse.

This article discusses the forensic medical decision-making process in cases of alleged recent (usually up to 72 hours) sexual assault of a victim unable to consent. Our aim was to identify possible ethical problems that can arise in this context, analyze its components, and argue about which elements should be considered by forensic medical doctors when deciding whether to perform the examination and/or report the alleged crime to legal authorities.

LEGAL FRAMEWORK

Legal provisions dictate that expert evidence (in the form of report or testimony) is essential whenever specific knowledge in a particular scientific field is necessary to assess the facts related with a crime. If such field is Medicine, a medico-legal examination should take place.[5]

Medico-legal examination

Respecting the autonomy of examinees is a critical topic in our discussion. The Portuguese Criminal Code and the Law 45/2004 of August 19th, which establishes the legal framework of medico-legal examinations, describe the subjects' obligation to undergo a forensic medical examination if deemed necessary to the investigation or pre-trial phases of a criminal proceeding, provided that a competent legal authority ordered it. The rights and values protected by criminal law may justify a (proportional) restriction of individual rights, namely to bodily and moral integrity.

There are many examples, in distinct judicial contexts, of the obligation to provide biological samples (blood or others) and/or to be evaluated by a medical doctor. The Road Traffic Code[6] and Law-decree 15/1993 of January 22nd on illicit drug trafficking consider the possibility of compulsory blood/urine collection for alcohol or another drug determination. A medical examination may be requested when deemed useful.

The examinee's refusal to undergo to such tests constitutes a crime of disobedience. Moreover, the physician who refuses to perform the necessary examinations without a valid reason is legally punished for disobedience. In short, the Portuguese law states not only that the examinees are obliged to undergo a forensic medical examination but also that physicians (and other healthcare professionals) have a duty to ensure that the technical procedures required to preserve evidence are carried out. How should we deal with refusal of consent in this context?

The Ethical Code of the Portuguese Medical Association states that medical doctors must comply with all deontological principles even when performing medico-legal examinations. In its 103rd article, this Professional Code of Ethics highlights that medical doctors should not perform a medico-legal examination if the examinee does not provide consent. It is also stated that pharmacological or other methods that may impair the examinee's volitional capacities cannot be used.[7] Both the Portuguese Constitution, in its 33rd article and the Criminal Procedure Code in its 126th article, assume that the evidence obtained through torture, coercion, physical or psychological harm or by abusive privacy intrusion is not valid and cannot be used in court.

The 150th article of the Portuguese Criminal Code states that interventions and treatments which, according to the state of knowledge and experience of medicine, are indicated and carried out, in accordance with *leges artis*, by a medical doctor or another legally authorized person, with the intention of preventing, diagnosing, debating or reducing disease, suffering, injury or bodily fatigue, or mental disturbance cannot be considered an offense to physical integrity, regardless of its outcomes.[8] But it may be considered a crime against freedom if the clinical intervention is performed without the patient's consent.[9]

The main aim of a forensic medical examination is to collect evidence (and only indirectly to prevent, diagnose or treat diseases). Such conducts can be considered a bodily harm offence if performed without the examinee's consent. The 149th article of the Portuguese Criminal Code allows interventions that may cause bodily harm to other people upon their consent, provided that the motives and purposes of the agent or the victim are taken into account, as well as the means employed and the foreseeable extent of the offense. Accordingly, forensic medical doctors have not only an ethical but also a legal duty to obtain consent prior to their intervention. Since forensic and clinical interventions have distinct objectives, having consent to perform a clinical intervention does not imply that the forensic intervention has also been consented and *vice versa*. It is essential to explain to the examinee the scope and the aims of the forensic examination and mention the duty to notify the legal authorities about its results.[10]

The examinee usually signs an informed consent form allowing the physical examination and evidence collection to be made and the biological samples to be analyzed. Young age and temporary or permanent cognitive impairment (due to mental health disorder or acute drug/alcohol intoxication) may render the examinee unable to provide a valid consent. Moreover, forensic medical doctors may have to decide whether the alleged crime should be reported to legal authorities even if the victims or their representative (for example when the legal representative is also the alleged offender) do not consent to the medico-legal examination or do not want to file a criminal complaint.

For these reasons, some authors argue that legal authorities may coercively lead the subject to undergo a

medico-legal examination.[11] If the subject still refuses to undergo the examination, the forensic medical doctor should not endanger the examinees' physical and moral integrity. However, (s)he must be informed about the consequences of such refusal since it will interfere with the criminal investigation.

Reporting the alleged crime

The need to report an alleged crime to legal authorities is another important issue to address. When legal authorities or civil servants become aware of a crime within the context of their professional activity they must report it.[12] Therefore, medical doctors working in the Portuguese National Health Service have the duty to report sexual crimes particularly when the criminal procedure does not depend on a complaint or an accusation (public crimes). In addition, there is still an ethical duty to report a sexual crime in private medical practice.

The Portuguese law states that some crimes should be reported regardless of the victim's will (public crimes). That is the case, for example, of domestic violence that includes sexual assault within an intimate relationship according to the 152nd article of the Portuguese Criminal Code and sexual abuse if the victim is a child or another legally incompetent person or a person held in a health institution. These victims are particularly vulnerable due to their age and/or cognitive impairment and/or the type of relationship they have with the offender.

When deliberating about such issues one must question if there is reasonable suspicion and whether reporting is the right thing to do (Fig. 1). Whenever there are reasons to suspect that a crime was committed, the forensic medical doctor has the duty to perform a medical examination. However, the medical examination does not always confirm or rule out the 'diagnosis' of sexual abuse promptly. In fact, there are some physical findings that are specific of sexual abuse (for example pregnancy at a young age), with the majority being ambiguous and often inconclusive. Furthermore, absence of physical findings does not rule out abuse since it does not always cause visible injuries, and when it does, these may rapidly heal. The analysis of biological samples may later confirm recent sexual activity/contact even when physical evidence supporting the abuse allegations were absent. For these reasons, the decision to report the case after performing the forensic medical examination is not easy.

Reporting does not (and should not) demand clear evidence of abuse but should follow reasonable suspicion since a legal intervention brings stress into people's lives, often disrupting family unity. There is no specific guidance in this field and there are currently different perspectives about when to report.[13,14] In addition, the existence of conflicting data that increases uncertainty is common. It is important to analyze the circumstances that raised the suspicion and determine the factors that should be considered when assessing the likelihood that a legally (temporarily or permanent) incompetent person has been sexually abused.

ANALYSING CIRCUMSTANCES TO IDENTIFY ETHICAL PROBLEMS

Moral dilemmas or problems usually arise in circumstances where the agent has (or apparently has) a moral obligation to perform two or more mutually exclusive courses of action. Since the individual cannot perform all the required courses of action simultaneously, (s)he faces a moral conflict. There are also cases where the agent finds facts suggesting that a particular course of action is morally permissible and other facts (with similar strength) indicating that the same course of action is morally wrong.[15]

Gracia highlighted that ethical deliberation is the answer to solve such conflicts between moral values and/or deontological duties.[16] The deliberation process is based on facts that support values. Such (moral) values support both duties and responsibilities (professional, legal and social). In each step of the ethical deliberation, the values and duties in conflict should be weighted according to their importance under the circumstances.

Whenever the victim is not able to consent the deliberation about whether to proceed with the medico-legal examination one must first consider the available circumstances and facts such as the reasonableness of the allegations, the characteristics of the alleged sexual abuse and the ones of the victim and her/his relationship with the offender (Fig. 1). For example, if the type of the abuse may leave physical or biological evidence, the urgency to preserve/collect evidence may justify performing the examination when consent cannot be obtained.

Legally incompetent victims

The victim of sexual abuse may not be able to consent due to one's age or a clinical reason that warrants legal incompetency. When their legal guardian does not consent to the medico-legal examination, legal authorities should be notified promptly.[17] The need to collect/preserve evidence may justify carrying out the examination immediately. Recent injuries (in particular at the hymen and mucosal surfaces of body cavities), depending on their severity, may heal rapidly. Biological samples, such as saliva and/or sperm (that may be used to identify the offender's DNA profile which in turn can be compared with the suspect's) may degrade quickly or be lost or destroyed.

Consent for minors is valid from 16 years old if one has the capacity to understand its meaning and extent.[18] But their right to be heard and to have his or her views considered, in decisions that affect them, should be respected according to their age, level of understanding and maturity. For example, the Law 112/2009, of September 16th, which provides the legal framework for the prevention of domestic violence, states that the interventions assisting children under 16 years of age who suffered domestic violence should be preceded by his/her legal guardian's consent. When the physician is unable to contact the legal guardian or (s)he is the alleged offender, the public prosecutor's office may be consulted. The will of a child over the age of 12 years should also be considered according to his/her cognitive

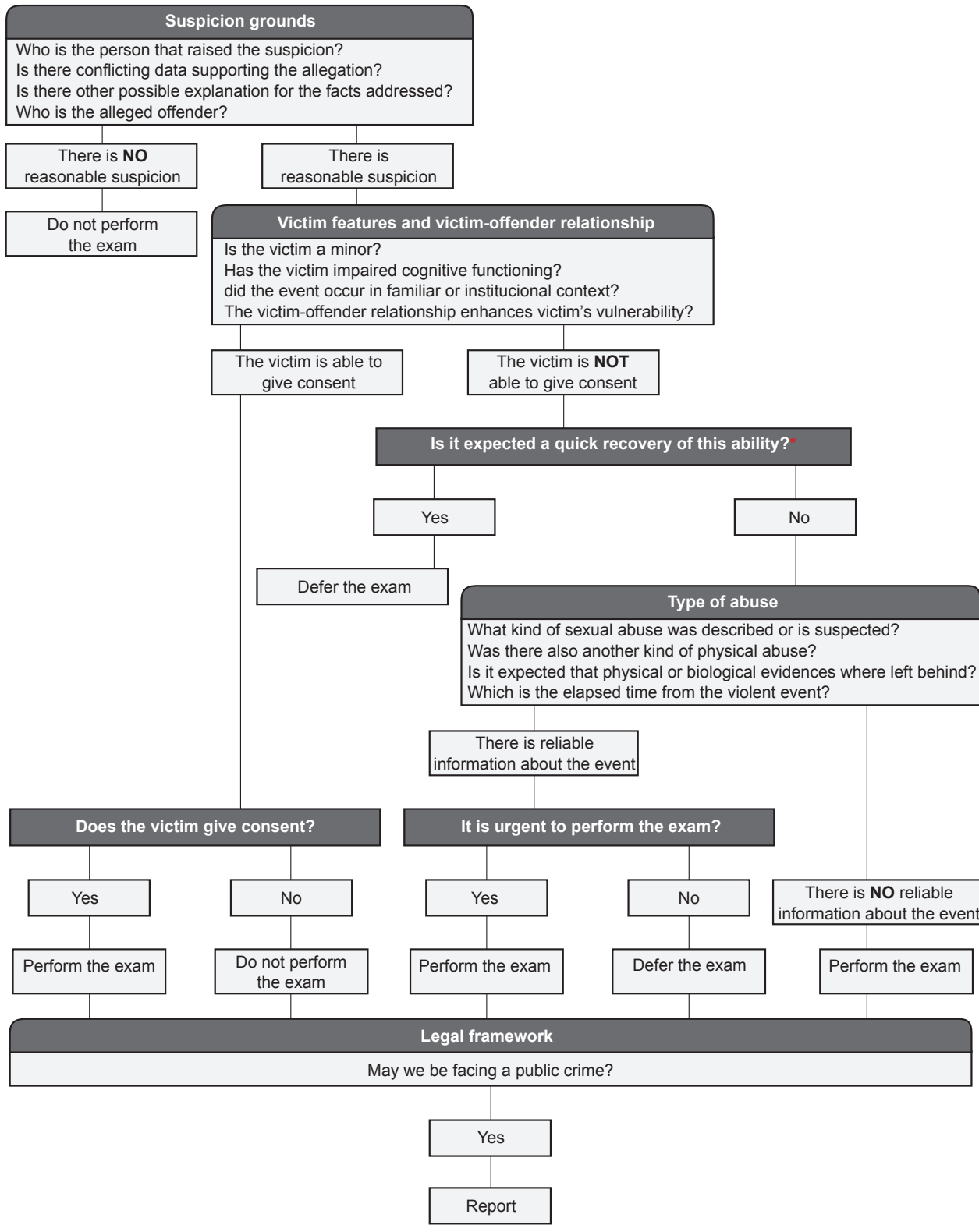

Figure 1 – Decision-making tree

* The interventions assisting children under 16 years of age should be preceded by his/her legal guardian's consent. When physician is unable to contact the legal guardian or (s)he is the alleged offender the physician may consult with the public prosecutor's office.

competences. Legally incompetent persons over 16 years old should also participate in the decision-making process, whenever possible.[19]

Concerning interventions to assist children under 16 years of age who suffered domestic violence, the Law 112/2009 of September 16th states that when it is not

possible to obtain the legal representative's consent in due time or (s)he is the alleged offender and is not possible to obtain the legally approved entities' consent in due time, the consent from children over the age of 12 years is enough.[20]

In the healthcare field, the emancipation granted to teenagers is notorious. The area of reproductive health is not an exception since the 5th article of Law 3/1984 of March 24th [21] grants full access to medical care and other family planning means to all the population, including teenagers. Therefore, an exception is made regarding parental decision in any issue concerning minors' sexual health and contraception choices.[5] The respect for a person's autonomy is coupled with the respect for his/her privacy, a fact that frequently encourages the medical doctor not to disclose certain information regarding these matters to parents or legal guardians, thus serving the minor's interests.

We know that any event behind the forensic medical examination of a child, namely sexual abuse, can cause important emotional imbalance and frailty. In this context, the forensic examination may be understood as an aversive stimulus leading to avoidance conducts. The medical doctor must provide detailed information about the forensic procedures and their objectives and must be receptive to answering questions, in order to allay fears and uncertainties. It is essential to consider that the examinee is particularly vulnerable since the autonomy impairment due to young age is increased by the fact that (s)he was a victim of a crime. As stated by Ricoeur, vulnerability makes autonomy only a condition of possibility.[22]

In other cases, the legal representative consents to the medico-legal assessment but the child or the legally incompetent person does not allow the medical examination, sometimes offering physical opposition (for example due to cognitive immaturity or impaired development). Under the principle of beneficence, the examination may be essential to understand what really happened and guide the adoption of protective psychosocial measures, promoting his/her emotional balance and harmonious development. Anyway, in this context, performing the examination may endanger the examinee's physical and moral integrity, thereby violating the principle of nonmaleficence. Whenever the allegations are plausible (this issue is important to assess since in most of these cases the victim provides little information), it could be appropriate to use a sedative, provided that the procedure does not put the examinee's health at risk. Accordingly, the administration of this medication should be performed and monitored by a medical doctor such as a pediatrician. Article 105 of the Code of Ethics of the Portuguese Medical Association states that the forensic medical doctor cannot use methods or substances that may impair the examinees' volitional capabilities. However, in this particular case, the aim of the forensic medical doctors is to promote the wellbeing of the examinees during the examination and not to supersede his/her will.

In the medical forensic setting, there are also other ethical 'doubts'. For example, allegations of sexual abuse during child custody disputes are common. In familiar environments that is expected to occur, especially between parents and young children, bed-sharing or touching the child's genitalia (when carrying out tasks such as dressing, bathing and changing diapers). Sometimes the allegations of sexual abuse arise from exaggerated attention given to that kind of daily activities, particularly if performed by the parent of the opposite sex. In fact, when one parent is suspicious of the other, his/her behavior may transfer the concern/apprehension towards the child's behavior either intentionally or unintentionally, for instance when asking relentlessly about everything that happened in his/her absence.[23,24] In such example, the child may be brought to the hospital every time (s)he returns from the home of the allegedly abusive parent meaning that the forensic medical examination procedures, which encompasses forensic interview, physical examination and biological sample collection, may become repetitive. This fact raises serious issues about secondary victimization (since behaviors and practices that legal medical personnel engage in may unconsciously be victim-blaming and/or enhance the victims' psychological trauma), thus seriously compromising the ethical principle of nonmaleficence. Once again, the forensic medical doctor must be careful when deciding whether to reexamine the child. It is important to consider elements such as the time elapsed since the last examination, whether biological samples were collected and whether the results/conclusions of the previous examinations are already available. Whenever the child is able to describe the abusive event, such information may also help to decide whether the replication of the medical examination is able to highlight new evidence according to the described circumstances.[25,26]

Other incompetent victims

There are cases where a competent person over 16 years old is, for some reason, temporarily unable to consent. When it is urgent to perform a medico-legal evaluation, the medical doctor finds a conflict between the examinees' individual rights and the legal and public interests to find justice. In the hospital emergency setting we may find patients unable to consent due to, among other reasons, acute alcohol or drug intoxication, loss or impairment of consciousness or acute exacerbation of a mental disorder. In this context, the medical doctor must evaluate the situation whenever there are signs, symptoms or circumstances suggesting recent sexual assault such as: witnessed sexual abuse, the examinee being partially or totally undressed or wearing underwear inside out without any reasonable explanation, the examinee's clothes being torn or his/her head or pubic hair shaved, the presence of human bite marks, ligature marks or burn injuries in the examinee's body surface, acute anogenital injuries, signs of attempted strangulation, and/or reasonable suspicion (or knowledge) that the examinee is a victim of intimate partner violence.[27]

The medical forensic examination should be deferred if the patient's behavior puts his/her own physical integrity at risk and if a quick recovery of cognitive abilities is anticipated (for example in cases of acute alcoholic intoxication).

Likewise, the medical doctor and any other healthcare professionals performing the forensic examination should not put their physical integrity at risk.[28]

In face of uncertain prognosis and/or when there is a real risk of destruction of evidence through clinical procedures, such as urethral catheterization, or washing the hair and body surface, the forensic medical examination is legitimized. Furthermore, biological samples may deteriorate over time or be lost (for example if the victim eats, urinates or defecates).

In such cases, an ethical problem is raised since the medical doctor must respect the person's autonomy and, considering health in its broader sense of biopsychosocial wellbeing, promote the health of the examinees under the ethical principle of beneficence. In fact, preserving evidence may serve the best interest of the examinee since that may allow the identification or conviction of the offender, which can directly or indirectly affect the victim's wellbeing. In such instance, we may consider that there is a presumed consent since the situation allows the medical doctor to reasonably assume that the examinee would have consented to the forensic medical examination if permission could have been sought, as stated in the article 39 of the Portuguese Criminal Code.

The legal background of the case should be assessed whenever possible. Provided that the sexual assault did not cause the death of the victim over 16 years old, the criminal procedure is usually dependent on his/her complaint. Therefore, if the victim recovers the self-determination abilities, (s)he will be able to decide whether the criminal investigation should be continued, namely using the evidence preserved during the medico-legal examination.[28] If the forensic medical doctor did not preserve the evidence, since the victim was temporarily unable to consent (namely in situations where a quick recovery of this ability is not expected), the legal investigation will be compromised. That may prevent an autonomous choice when (s)he finally recovers her/his cognitive abilities.

On the other hand, when the offender is in an intimate relationship with the victim, the criminal procedure may take place regardless of the victim's will (public crime). There is a need to promote the victim's protection because (s)he is in a particularly vulnerable situation, and is often emotionally and financially dependent.[17]

Gracia believes that the ethical principle of nonmaleficence has a public nature, meaning that it must be formulated in an acceptable way to everyone or at least the majority. The obligation of the forensic medical doctor is to protect the examinee's psychological and physical health. The principles of autonomy and beneficence, being of a private nature, may be observed according to the circumstances of the particular case.[16]

PROPOSAL FOR PRATICAL ACTION

Medical decision-making is a complex task within the doctor-patient relationship that encompasses clinical, legal and ethical criteria having also, to some extent, anthropological traits. In forensic medicine, when handling cases of alleged sexual assault, medical doctors face additional difficulties regarding the decision-making process. In this context, there are many variables and features influencing the decision and the different issues of the problem must be addressed individually.[4]

The decision-making process about whether the forensic medical doctor should perform an examination and/or report the crime when assessing an alleged victim of sexual abuse may encompass multiple dimensions such as (Fig. 1):

- Suspicion grounds: Who is the person that raised the suspicion? Is there conflicting data that may weaken the allegation? Or is there another possible or reasonable explanation for the facts addressed by the medical doctor? Who is the alleged offender?
- Victim features: Is the victim a minor? Has the victim impaired cognitive functioning? If not, is the victim competent to provide consent in that moment? If not, is the victim permanently or temporarily incompetent?
- Victim-offender relationship: Did the act of violence occur in familiar or institutional contexts? Does the type of relationship enhance the victim's vulnerability?
- Type of abuse: What kind of sexual abuse was described or is suspected? Was there also another kind of physical abuse? Is it expected that physical or biological evidence was left behind? What is the elapsed time from the violent event?
- Legal framework: May we be facing a public crime? Are there previously filed reports against the alleged offender?

There must be an immediate articulation between medico-legal services, legal authorities and victim-support organizations to gather all the important elements and information so that the victim could be adequately protected, and the alleged perpetrator prosecuted.

CONCLUSION

In the forensic field, medical doctors may face many ethical problems namely when assessing alleged victims of sexual assault. It is not possible to foresee every possible course of action and its consequences regardless of how detailed our evaluation of the case may be. In this background of uncertainty, the medical assessment of the case does not always point out an unequivocal legal or ethical duty to perform the forensic examination and/or report the alleged crime to the legal authorities. The ethical deliberation process is critical for choosing a reasonable course of action and make decisions that couple technical expertise with human virtues. In fact, the role of medical doctors in this context is not solely to ensure the victim's privacy during the physical examination and/or perform medical interventions, but also to promote the respect for human dignity encompassing all fundamental principles of medical ethics in their practice within the scope of the expert assistance required by the justice system.

Professional ethical codes are not enough to guide medical practice. They highlight important issues to consider in medical practice but do not (and should not) strictly point out the right courses of action. Medical doctors must have ethical theoretical grounds and should understand moral concepts and the ethical framework of medical practice. This 'ethical awareness' facilitates the process of decision-making. enabling medical doctors to recognize ethical problems and solve them adequately.[29,30] A broad understanding of medical ethics is essential to differentiate right from wrong according to the circumstances of the case in order to avoid overlooking important ethical issues or applying general rules in ethical decision-making blindly. If medical doctors overlook an important ethical issue they may fail to act when they should. If they apply general ethical rules blindly, they will not engage in the necessary balancing process that guides ethical decision-making or dictate which ethical values or principles should prevail in a given case.

AUTHOR CONTRIBUTIONS

BSR: Design, draft and conception of the work, critical review and final approval of the version to be published.

MS, DNV, FCR: Conception of the work, critical review and final approval of the version to be published.

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COMPETING INTERESTS

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The Dark Side of the Tongue: The Stomatology Point of View on Oral Hyperpigmentation

O Lado Negro da Língua: O Ponto de Vista da Estomatologia sobre Hiperpigmentações Orais

Keywords: Hyperpigmentation/chemically induced; Temozolomide/adverse effects; Tongue Diseases/chemically induced
Palavras-chave: Doenças da Língua/induzida quimicamente; Hiperpigmentação/induzida quimicamente; Temozolomida/efeitos adversos

Dear Editor,

We read with great interest a case report about tongue hyperpigmentation associated with temozolomide as a single agent.[1] In the article, the authors point out the uniqueness of the case since temozolomide was the only drug causing oral hyperpigmentation, which was never reported, as well as its relevance for healthcare professionals regarding pharmacological side effects of specific drugs.

Oral hyperpigmentation can cover a broad spectrum of diagnoses that may include physiological variations associated with ethnic differences, with a predominance in dark-skinned populations, benign lesions such as amalgam tattoos, oral repercussions due to systemic disease, such as Addison's disease, malignant lesions such as oral melanoma and, as stressed by the authors, an adverse effect of pharmacological therapy.[2]

In the literature, oral and skin hyperpigmentation due to chemotherapy has been well-documented.[2,3] One of the most common drugs associated with oral pigmentation is the tyrosine kinase inhibitor, imatinib, commonly used in chronic myeloid leukemia. Additionally, studies report that treatment duration or the synergic effect in patients who had treatment with hydroxyurea before commencing imatinib therapy are risk factors for more extensive and darker lesions.[2]

In this case, the onset of hyperpigmentation was related to the initiation of temozolomide. However, an evaluation by a stomatologist might aid the diagnosis by discarding other possible diagnoses or factors, although less likely, that might contribute to the oral pigmentations, for example, amalgam tattoos or chewing tobacco, which can mimic the observed lesions. Additionally, levetiracetam has already been reported as being associated with cutaneous hyperpigmentation.[4] While that report does not mention the oral mucosa, oral hyperpigmentation due to this drug could not be discarded, including a synergetic effect with temozolomide. Antiepileptic drugs like oxcarbazepine or retigabine have already been reported to induce oral pigmentation.[5]

Diagnosis of oral pigmented lesions is challenging, with definitive diagnosis typically requiring histopathological examination. Although most hyperpigmented lesions are benign, diagnosis based on a detailed history and clinical examination alone only provides a provisional diagnosis. Clinicians may consider the use of biopsy, especially in less suggestive cases. As an adverse effect, oral hyperpigmentation is innocuous, but surveillance is advised in order to monitor changes in lesions over time.[2]

Physicians must be aware of pigmented oral lesions while treating cancer patients. We advise referral to the Department of Stomatology, in which the clinician wants to ensure their clinical suspicion, exclude contributing factors, or rule out other lesions of a malignant nature.

AUTHOR CONTRIBUTIONS

RS: Draft of the paper, approval of the final version.
NR, CM: Critical review, approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

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The authors have declared that no competing interests exist.

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COVID-19 e Diabetes Mellitus: O Impacto de Duas Pandemias

COVID-19 and Diabetes Mellitus: The Impact of Two Pandemics

Palavras-chave: COVID-19; Diabetes Mellitus; Hipoglicemiantes; SARS-CoV-2
Keywords: COVID-19; Diabetes Mellitus; Hypoglycemic Agents; SARS-CoV-2

A enzima conversora da angiotensina-2 (ACE2) funciona como recetor para a proteína *spike* do SARS-CoV-2, facilitando a sua entrada nas células.[1] Esta enzima é expressa também no pâncreas, podendo levar a diabetes inaugural após a infeção por SARS-CoV-2. Além disso, por ação do vírus, ocorre diminuição da secreção de insulina (por lesão direta da célula beta) e aumento da insulino-resistência.[1] Aquando da infeção por SARS-CoV-2 era frequente a ocorrência de um estado pró-inflamatório, com risco de 'tempestade imunológica', que muitas vezes constituía o evento final da evolução da doença e que era mais frequente em doentes com diabetes.[2] A vacinação veio alterar o paradigma, diminuindo a frequência com que este fenómeno imunológico ocorre através do controlo precoce da infeção.[3]

Assim, a diabetes *mellitus* (sobretudo se descompensada) pode conferir severidade à COVID-19.[2] Por outro lado, a infeção por SARS-CoV-2 potencia a hiperglicemia e o descontrolo metabólico, perpetuando um círculo vicioso que acrescenta risco ao doente e pode agravar o prognóstico.

Em epidemias anteriores, os doentes com diabetes pareciam ter maior risco de contrair a doença[2]; não parece ser o caso da COVID-19.[4] Porém, no que respeita à severidade, os doentes com diabetes são mais frequentemente hospitalizados, têm maior risco de admissão em cuidados intensivos (CI) e maior mortalidade.[1,2] Tanto a glicose à admissão como a hiperglicemia ao longo do internamento se associam a piores *outcomes*.[2,5] O controlo glicémico prévio também se relaciona com o prognóstico – pior controlo implica maior mortalidade.[2] Além disso, os doentes com COVID-19 têm maior risco de cetoacidose diabética (CAD) e síndrome hiperglicémico hiperosmolar (SHH).[6]

Em doentes internados com COVID-19, a insulina é o fármaco de escolha.[7] O uso prévio de metformina foi associado a menor mortalidade; os agonistas da enzima GLP-1 e as glitazonas também foram associados a potenciais efeitos benéficos em doentes com COVID-19, mas mais estudos são necessários.[7]

Propomos assim os seguintes princípios relativamente ao doente com diabetes infetado com SARS-CoV-2:

1. Os doentes com diabetes não têm maior risco de contrair COVID-19.
2. Os doentes com diabetes têm maior risco de COVID-19 severo.
3. Os doentes com diabetes internados com COVID-19 devem suspender a toma de antidiabéticos orais, sendo a insulinoterapia a opção terapêutica.
4. Os doentes com diabetes e com COVID-19 em ambulatório podem manter os antidiabéticos orais, com monitorização apertada da glicose.
5. A metformina, os agonistas da GLP-1 e as glitazonas poderão ter efeito benéfico na COVID-19.
6. O SARS-CoV-2 pode afetar o pâncreas e levar a diabetes *de novo* após a infeção – é necessário avaliar os doentes tendo em conta essa possibilidade.
7. O mau controlo metabólico prévio associa-se a pior prognóstico.
8. A hiperglicemia no internamento está associada a maior mortalidade, mesmo em não diabéticos – o controlo precoce e rigoroso da glicemia é essencial.
9. Um elevado número de doentes com COVID-19 desenvolvem CAD/SHH. É necessária especial atenção aos indivíduos sob corticoterapia. Estes doentes exigem controlo glicémico apertado assim como avaliação gasométrica e de cetonemia frequentes.
10. Doentes com diabetes e com COVID-19 têm necessidades muito superiores de insulina.

No geral, estas recomendações mantêm-se atualizadas mesmo com a maioria da população vacinada. Com a vacinação, a maioria dos efeitos negativos da COVID-19 foram reduzidos, mas não eliminados. Assim, é importante priorizar os doentes com diabetes na administração das vacinas contra o SARS-CoV-2, independentemente do tipo de diabetes e da idade.[8]

CONTRIBUTO DOS AUTORES

PO, JL: Redação do artigo; pesquisa bibliográfica.
PG, LA: Revisão do artigo.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

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Professionals as Targets in the Culture Wars: A European Perspective

Profissionais de Saúde como Alvo da Guerra Cultural: Uma Perspetiva Europeia

Keywords: Culture; Dissent and Disputes; Europe; Health Personnel; Sexual and Gender Minorities

Palavras-chave: Cultura; Dissidência e Disputas; Europa; Minorias Sexuais e de Género; Pessoal de Saúde

I read with both fear and hope the article where Hadland[1] describes the current process of shaping the public narratives in the United States against lesbian, gay, bisexual, transgender, queer or questioning (LGBTQ) people.

LGBTQ, and trans people in particular, face high levels of discrimination and violence worldwide. In Europe there are significant problems in Hungary and Poland[2] and, even in more liberal countries, both mainstream and social media are increasingly flooded with anti-LGBTQ opinions. The Portuguese Medical Association, for example, still has no initiative specifically targeting LGBTQ individuals or professionals. Furthermore, LGBTQ issues are underrepresented in Portugal's most influential general medical journal (*Acta Médica Portuguesa*) with only three articles specifically addressing LGBTQ health-related issues published in the last ten years.

A recent study pointed out that only 13 out of 31 European countries have legislation that offers protection based on gender identity and/or sex characteristics.[3] The increasing politicization of healthcare is potentially dangerous, and may contribute to hinder access to evidence-based care, increasing mental health-related problems, and to decreased well-being among LGBTQ individuals.

The time to act is now. We need the medical community, professional organizations, health and scientific institutions, national governments, and European organizations[4] to act quickly to protect LGBTQ individuals and professionals from harassment and discrimination.

PROTECTION OF HUMANS AND ANIMALS

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COMPETING INTERESTS

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The Implementation of a PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) Program in Portugal

A Implementação de um Programa de PIPAC (Quimioterapia em Aerossol Intraperitoneal Pressurizada) em Portugal

Keywords: Aerosols/administration & dosage; Antineoplastic Agents/administration & dosage; Hyperthermic Intraperitoneal Chemothe-rapy; Peritoneal Neoplasms/drug therapy

Palavras-chave: Aerossóis/administração e dosagem; Antineoplásicas/administração e dosagem; Neoplasias Peritoneais/tratamento farmacológico; Quimioterapia Intraperitoneal Hipertérmica

Dear Editor,

Last June, Centro Hospitalar Universitário de São João started a pressurized intraperitoneal aerosol chemotherapy (PIPAC) program, having treated three patients until now.

Despite all the therapeutic advances in oncology, with remarkable survival improvements in different cancers, peritoneal metastasis (PM) continues to be a challenging field with no efficient therapeutic options, other than for a few patients with limited disease that can be candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). However, the majority will have extensive disease that prevents this strategy.[1]

A theory that tries to explain the poor prognosis and the lack of a valid therapeutic option for PM is called the 'plasma-peritoneal barrier'.[2] This phenomenon is similar to the blood–brain barrier, in which the diffusion of systemic drugs is limited. In 2011, Marc Reymond described an experimental treatment with an optimized technology for the peritoneal delivery of aerosolized chemotherapy.[3] It allows to overcome the limitation of systemic chemotherapy in terms of the drug distribution and poor penetration into peritoneal nodules, but also to improve the delivery of peritoneal chemotherapy compared to HIPEC. A PIPAC treatment consists usually of three sessions across a six-eight-week period. However, in patients with good response, the number of sessions can be extended.[1]

Due to the selection bias and lack of randomized trials, it is impossible to properly appraise the survival benefits of this approach. However, the results have been encouraging, with an objective tumor response according to the histological Peritoneal Regression Grading Score of around 70%[4] and, in some patients, with a reduction in PM that allows subsequent cytoreduction surgery and HIPEC.[1] The research around PIPAC has been focusing on optimizing the procedure as well as treatment regimen/doses to allow the development of clinical trials.

Even though the two surgeons involved in this program took part in the Scandinavian PIPAC Workshop in 2018 and 2019, the pandemic situation prevented this from happening until now. We are very pleased to have this treatment option now available for selected patients with PM from different cancers. In Denmark, all PIPAC procedures are centralized in one center, and we agree that a similar strategy should also be employed in Portugal, to allow the accrual of crucial knowledge and expertise about this treatment. We are collaborating with other PIPAC centers around the world[5] and have a dedicated multidisciplinary team to evaluate candidate patients referred to our center for this new treatment approach.

AUTHOR CONTRIBUTIONS

TBM: Conception of the original idea; writing of the manuscript.

MA, SM, MG, EB: Revision of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

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Síndrome do Linfócito Passageiro Após Transplante Hepático: Uma Entidade Causadora de Anemia Hemolítica

Passenger Lymphocyte Syndrome After Liver Transplantation: A Cause of Hemolytic Anemia

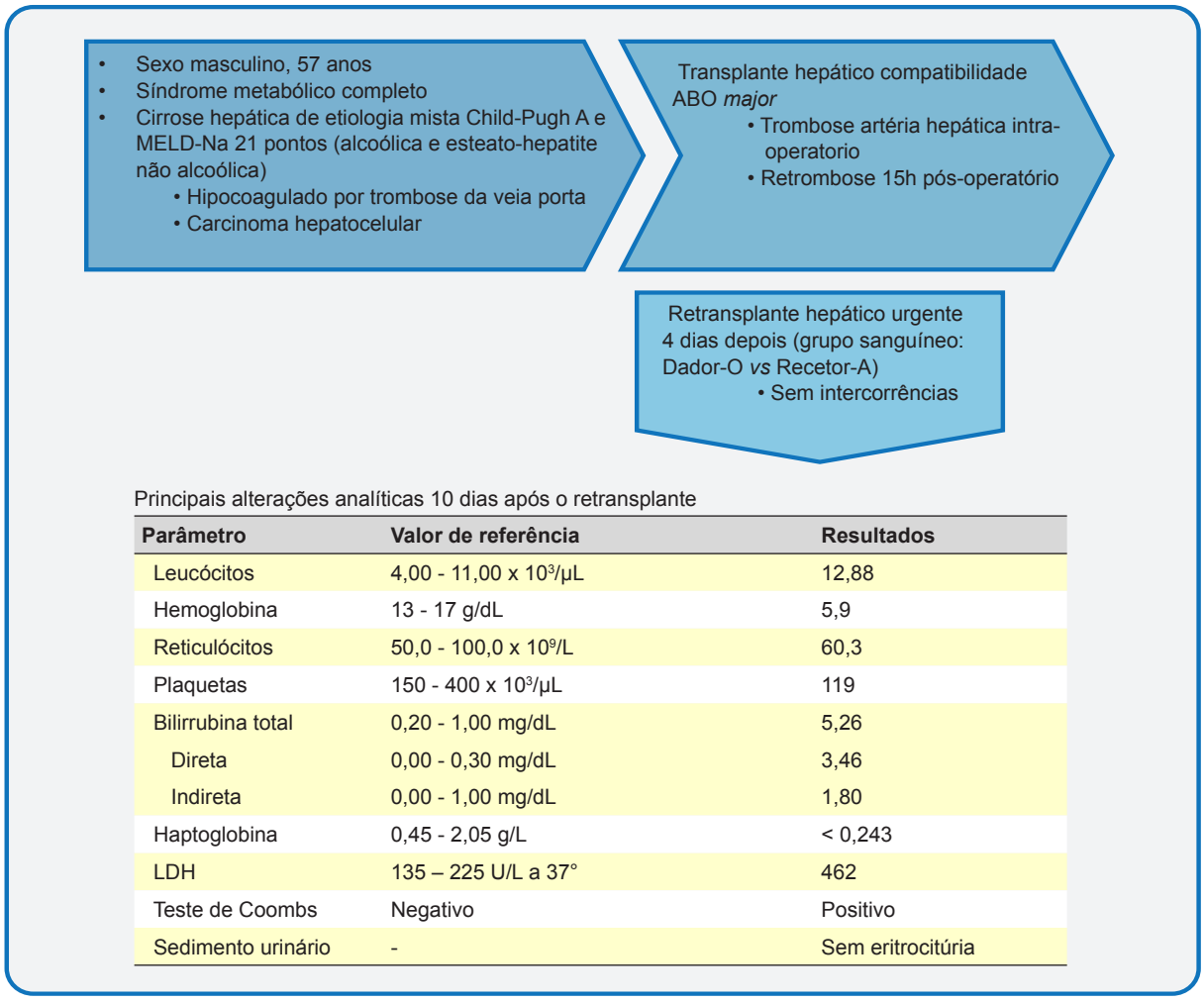
Palavras-chave: Anemia Hemolítica/etiologia; Sistema de Grupo Sanguíneo ABO; Transplante de Fígado/efeitos adversos
Keywords: ABO Blood-Group System; Anemia, Hemolytic/etiology; Liver Transplantation/adverse effects

A anemia é comum em qualquer pós-operatório. Em particular no pós-transplante, há que lembrar diagnósticos diferenciais. As causas mais comuns são, até à segunda semana, a hemorragia, sépsis e complicações locais (trombose da artéria hepática ou das veias cava inferior/hepática/porta e vias biliares); entre a segunda e a sexta semana, a anemia aplástica, infeções por citomegalovírus (CMV) ou parvovírus e doença do enxerto contra o hospedeiro (DECH); após as seis semanas, as causas mais comuns são défices vitamínicos, doença linfoproliferativa pós-transplante e multifatorialidade.[1,2] Os fármacos recomendados são agentes tempo-independente, sendo de salientar imunossupressores como o tacrolimus, que está associado à anemia hemolítica microangiopática.[1,2] À semelhança do que acontece em doentes não transplantados, esta última pode ser também secundária a infeções ou imunomediada.[1,2] A etiologia hemolítica ocorre entre o terceiro e o 24.º dia sendo habitualmente auto-limitada, mas podendo evoluir de forma fatal.[1,2]

O caso clínico de síndrome do linfócito passageiro (SLP) após transplante hepático que espelhamos na Fig. 1 motivou a reflexão sobre esta entidade.

Dada a lista de espera para transplante hepático *versus* o número de órgãos disponíveis, o transplante hepático é por vezes realizado com incompatibilidade ABO *minor*, nomeadamente no caso de dador vivo, falência hepática aguda, doentes do tipo AB ou retransplantes urgentes.[3-5] Nestes casos, a SLP é um tipo de DECH relativamente comum e tende a ser subdiagnosticada, pois não é observada frequentemente por clínicos não dedicados à transplantação. Os doentes nesta situação acabam por recorrer, naturalmente, a qualquer unidade de cuidados de saúde, sendo importante que todos os médicos tenham conhecimento desta síndrome. A SLP ocorre por incompatibilidade ABO *minor*, em que os linfócitos B do dador produzem anticorpos contra os antigénios dos eritrócitos do hospedeiro, levando à sua *lise*.[3,5] A SLP é mais frequente nos transplantes de coração e pulmão (70%), fígado (40%) e rim (17%) respetivamente, dada a maior quantidade de tecido linfoide transplantado.[3-5]

O tratamento é de suporte com transfusão de sangue



Principais alterações analíticas 10 dias após o retransplante

Parâmetro	Valor de referência	Resultados
Leucócitos	4,00 - 11,00 x 10^3/µL	12,88
Hemoglobina	13 - 17 g/dL	5,9
Reticulócitos	50,0 - 100,0 x 10^9/L	60,3
Plaquetas	150 - 400 x 10^3/µL	119
Bilirrubina total	0,20 - 1,00 mg/dL	5,26
Direta	0,00 - 0,30 mg/dL	3,46
Indireta	0,00 - 1,00 mg/dL	1,80
Haptoglobina	0,45 - 2,05 g/L	< 0,243
LDH	135 – 225 U/L a 37°	462
Teste de Coombs	Negativo	Positivo
Sedimento urinário	-	Sem eritrocitúria

Figura 1 – Caso clínico de SLP após transplante hepático

do tipo do dador ou do tipo O até que o teste direto de antiglobulina seja negativo.[4] Nos casos graves, poderá considerar-se a plasmaférese ou hemaférese (isto é, substituição dos anticorpos do dador ou especificamente dos glóbulos vermelhos do hospedeiro).[4,5] Há bons resultados descritos com rituximab; a eficácia das imunoglobulinas, corticoterapia ou o aumento da imunossupressão ainda não está esclarecida.[3,4]

Dado a anemia ser frequente no período precoce pós-transplante, relembramos este diagnóstico diferencial, já que requer um elevado nível de suspeição para poder agilizar a tomada de atitudes, nomeadamente corticoterapia e transfusão de glóbulos vermelhos do tipo do dador do órgão transplantado.

CONTRIBUTO DOS AUTORES

DIR: Pesquisa bibliográfica; escrita do manuscrito.
SF, HPM: Revisão do manuscrito.
MBA: Pesquisa bibliográfica; revisão do manuscrito.

CONSENTIMENTO DO DOENTE

Obtido.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

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Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Um Caso de Pneumonia Atípica por COVID-19 Grave e Reação Cruzada com *Coxiella burnetii*

A Case of Atypical Pneumonia Due to Severe COVID-19 and Cross Reaction with *Coxiella burnetii*

Palavras-chave: COVID-19; Coxiella burnetii; Febre Q; Infeção pelo SARS-CoV-2; Pandemia; Portugal; Reações Cruzadas
Keywords: COVID-19; Coxiella burnetii; Cross Reactions; Pandemics; Portugal; Q Fever; SARS-CoV-2 Infection

A 30 de janeiro de 2020 a Organização Mundial de Saúde (OMS) declarou a COVID-19 como uma emergência de saúde pública de importância internacional e, a 11 de março de 2020, caracterizou a doença como uma pandemia.[1] O primeiro caso de COVID-19 em Portugal foi diagnosticado a 2 de março de 2020. Contudo, a circulação prévia do vírus na comunidade adivinhava-se como possível.

Relatamos o caso de um homem de 44 anos, caucasiano, previamente saudável, que recorreu ao Serviço de Urgência de um hospital terciário em Portugal a 27 de fevereiro de 2020, por apresentar febre, tosse seca e mialgias com uma semana de evolução e agravamento progressivo. Negou contactos conhecidos com pessoas com sintomatologia semelhante, diagnóstico de COVID-19 ou viagens recentes. À admissão, encontrava-se febril (38,7ºC), taquicárdico (114 bpm), normotenso e com saturação periférica de oxigénio em repouso e em ar ambiente de 94%. A auscultação pulmonar revelou crepitações em ambas as bases. A radiografia torácica mostrou um infiltrado intersticial bilateral difuso. Analiticamente apresentou hipoxemia (PaO2 68,9 mmHg), hipocapnia (PaCO2 28,7 mmHg), linfopenia (0,67 x 10^9/L), elevação de lactato desidrogenase (409 U/L) e da proteína C reativa (1,09 mg/dL), tendo sido internado no serviço de Medicina Interna com o diagnóstico de pneumonia adquirida na comunidade.

No segundo dia de internamento houve agravamento clínico, com dispneia e dessaturação periférica, tendo sido identificadas alterações em vidro despolido na tomografia computadorizada do tórax. Os exames culturais de sangue e expetoração, pesquisa de vírus respiratórios e serologias para agentes de pneumonia atípica foram negativos, com exceção da serologia para *Coxiella burnetii,* que se revelou positiva - IgG 1,21, IgM 1,37 (limiar de deteção: 1,1). Foi feito o diagnóstico de febre Q aguda e o doente recebeu tratamento com doxiciclina, com melhoria progressiva, mas lenta. À data, por não reunir os critérios epidemiológicos, não foi realizado o rastreio de SARS-CoV-2.[2]

O doseamento de anticorpos anti-fase I e anti-fase II de *C. burnetii* foi negativo. Atendendo ao contexto pandémico, foram realizadas serologias para SARS-CoV-2 em amostras de plasma obtidas no internamento e armazenadas em seroteca, que revelaram IgG anti-SARS-CoV-2 anti-proteina do nucleocapsideo (NP) de 6,110 (limiar de deteção: 1,4) e IgM anti-SARS-CoV-2 de 61,100 (limiar de deteção: 1,1). Quatro meses após o internamento, o doente apresentava ainda títulos de anticorpos positivos (IgG anti--NP 3,290; IgM 3,590).

A sintomatologia respiratória associada a COVID-19 não difere da sintomatologia de outras infeções respiratórias agudas,[3] nomeadamente da febre Q aguda. Os métodos de deteção da COVID-19 tornaram-se progressivamente mais sensíveis e específicos.[4] A deteção de anticorpos IgG e IgM anti-SARS-CoV-2 (anti-proteína *spike* e anti- NP) permitiram verificar infeção passada e caracterizar a dinâmica da resposta imunológica individual.[5]

O diagnóstico retrospetivo de um caso de COVID-19, prévio ao primeiro caso documentado em Portugal por teste de amplificação de ácidos nucleicos evidencia a necessidade de elevada suspeição clínica perante uma doença emergente com rápida disseminação, agora e num futuro próximo, assim como a possível reação serológica cruzada do SARS-CoV-2 com *C. burnetii.*

CONTRIBUTO DOS AUTORES

CR: Observação e orientação do doente; redação do manuscrito; revisão do conteúdo científico.

FC: Redação do manuscrito; revisão do conteúdo científico.

CL: Fornecimento de dados; revisão do conteúdo científico.

EG: Observação e orientação do doente; revisão do conteúdo científico.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

FC recebeu pagamento ou honorários para palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educacionais da ViiV Healthcare e Gilead Sciences Portugal.

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