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AVALIAÇÃO DA ADEQUAÇÃO DE DOSE DE CEFEPIMA EM PACIENTES COM INSUFICIÊNCIA RENAL ADMITIDOS A UM SERVIÇO DE EMERGÊNCIA DE UM HOSPITAL UNIVERSITÁRIO

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Trabalho de Conclusão apresentado à
Residência Integrada Multiprofissional em Saúde
do Hospital de Clínicas de Porto Alegre
como requisito parcial para obtenção do título de Especialista
pelo Programa Adulto Crítico

.

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SUMÁRIO

1. INTRODUÇÃO

1.1 APRESENTAÇÃO DO TEMA

Devido ao aumento da resistência bacteriana, antibióticos de amplo espectro são cada vez mais utilizados para o tratamento de infecções. O cefepima é um destes, uma cefalosporina de quarta geração frequentemente empregada no tratamento empírico de infecções nosocomiais. A excreção do cefepima é majoritariamente renal, 85% da droga é eliminada em sua forma inalterada pelos rins (MAXIPIME, 2013; BARLAM et al., 2016).

A neurotoxicidade é uma complicação associada ao uso de cefepima, caracteriza-se por diversos sintomas neurológicos, como confusão, rebaixamento do nível de consciência mioclonias e convulsões. Estudos prévios sugerem a insuficiência renal como o principal fator de risco para a neurotoxicidade induzida por cefepima, principalmente quando as doses não estão devidamente ajustadas (APPA et al., 2017; PAYNE et al., 2017).

Estratégias para promover o uso de doses adequadas de cefepima em pacientes com insuficiência renal devem ser enfatizadas, estas devem abranger todas as unidades hospitalares. Atenção especial vem sendo despendida à promoção do uso adequado nos serviços de emergência. Superlotação, incerteza diagnóstica e falta de conhecimento sobre o paciente, são situações comuns no serviço de emergência, e que tornam este ambiente propício a prescrições inadequadas de antibióticos, incluindo a cefepima, as quais comumente são continuadas nas demais unidades hospitalares e podem levar a danos ao paciente (ARRABAL-DURÁN et al., 2014; PULCINI, 2014; ASÍN-PRIETO; RODRÍGUEZ-GASCÓN; ISLA, 2015; TRINH; KLINKER, 2015; BARLAM et al., 2016; LOSIER et al., 2017).

1.2 JUSTIFICATIVA

A necessidade de ajuste de dose da cefepima de acordo com a função renal do paciente a fim de evitar a ocorrência de neurotoxicidade, bem como estratégias para promover o uso de doses adequadas estão bem descritas. Estudos que avaliam a adequação de dose de cefepima em pacientes com insuficiência renal no contexto de serviços de emergência são escassos na literatura publicada e avaliam uma pequena amostra que não pode ser considerada representativa desta população.

No Serviço de Emergência Adulto do Hospital de Clínicas de Porto Alegre (EMA-HCPA) diariamente pacientes com múltiplas internações prévias e comorbidades, sendo a insuficiência renal uma delas, são admitidos para o tratamento de infecções. Muitos destes receberão tratamento com cefepima. A partir da impressão de que a cefepima é comumente prescrito em doses ou frequência inadequadas na EMA-HCPA, e considerando que estratégias podem ser empregadas a fim de corrigir tais inadequações já no início da terapia e assim evitar potenciais prejuízos aos pacientes, este estudo se justifica.

1.3 QUESTÃO DE PESQUISA

Doses adequadas de cefepima são prescritas a pacientes com insuficiência renal admitidos a EMA-HCPA?

2. REVISÃO DA LITERATURA

2.1 O SERVIÇO DE EMERGÊNCIA

Os atuais serviços de emergência (SE) possuem suas origens na década de 50, quando começaram a ser estabelecidos nos Estados Unidos. Destinam-se a oferecer cuidados rápidos e de alta intensidade a lesões e doenças agudas que ameaçam a vida do paciente. Entretanto, em algumas situações também prestam cuidados de atenção primária para aqueles que nunca tiveram ou que haviam perdido seu vínculo com os serviços de saúde (INSTITUTE OF MEDICINE, 2007). Desta forma, os SE servem como porta de entrada para o cuidado hospitalar, prestando cuidados a populações de alto risco, como doentes em estado crítico, pacientes oncológicos e aqueles com múltiplas comorbidades. Estima-se que, anualmente, uma em cada três pessoas irá precisar de atendimento em um SE. (AWAD; COCCHIO; BRIDGEMAN, 2016).

Algumas situações são rotineiras neste serviço, como: superlotação, alta rotatividade de pacientes, interrupções frequentes, realização de tarefas simultâneas, pressão para atender pacientes rapidamente, descontinuidade no cuidado, falta de familiaridade com os pacientes e de informações sobre os mesmos, e a necessidade de tomada de decisões rápidas. Todas estas contribuem para a ocorrência de erros relacionados ao cuidado em saúde. Dentre estes erros estão aqueles relacionados aos medicamentos, que atingem até 60% dos pacientes atendidos no SE (FAIRBANKS et al., 2004; SARD et al., 2008; PATANWALA et al., 2011; LIFSHITZ et al., 2012).

É essencial que estratégias de prevenção de erros relacionados a medicamentos sejam adotadas, a fim de evitar danos a saúde do paciente, bem como o aumento de custos relacionados ao seu cuidado hospitalar (FAIRBANKS et al., 2004; INSTITUTE OF MEDICINE, 2007; BROWN et al., 2008; PATANWALA et al., 2011). A presença do farmacêutico no SE tem sido proposta como uma destas estratégias. A atuação deste profissional multiplica as barreiras de proteção ao paciente, reduzindo a chance de potenciais erros acontecerem e alcançarem o mesmo (INSTITUTE OF MEDICINE, 2000; DECLIFFORD et al., 2007; BROWN et al., 2008; ACQUISTO; HAYS, 2015; AWAD; COCCHIO; BRIDGEMAN, 2016).

2.1.1 O farmacêutico no Serviço de Emergência

Os farmacêuticos passaram a estar presentes nos SE a partir da década de 70. O aumento significativo no número de emergências que contavam com a presença deste profissional ocorreu somente a partir de 1999, após a divulgação de um relatório elaborado pelo Institute of Medicine, que identificou o SE como ambiente de alto risco para erros relacionados a medicamentos. Desde então, a atuação do farmacêutico neste ambiente também se transformou, as atividades que eram focadas apenas na distribuição, gestão do estoque e dos custos de medicamentos tornaram-se clínicas, centradas no paciente, e à beira do leito (INSTITUTE OF MEDICINE, 2000; ACQUISTO; HAYS, 2015).

Atualmente, farmacêuticos ligados ao SE estão envolvidos em diversas atividades, como: revisão de prescrições, otimização da terapia medicamentosa, participação na tomada de decisões clínicas durante *rounds*, participação em procedimentos que utilizam medicamentos de alto risco, manejo de sedação e analgesia, preparo de medicamentos, fornecimento de informações sobre medicamentos, identificação de problemas relacionados a medicamentos, monitoramento de terapias medicamentosas, obtenção de história medicamentosa, e participação em atividades de *Stewardship* antimicrobiano (EPPERT; REZNEK, 2011; PATANWALA et al., 2012; PROPER et al., 2015; DAVIS et al., 2016; ROMAN et al., 2018).

Evidencia-se que as diversas ações desenvolvidas pelo farmacêutico no SE estão fortemente relacionadas a prevenção de erros relacionados a medicamentos. Os principais erros identificados por farmacêuticos são referentes a subdose e sobredose, sendo os antimicrobianos, os fármacos que atuam no sistema nervoso central (SNC), e os anticoagulantes e trombolíticos as principais classes de fármacos envolvidas nestes erros. Como resultado desta atuação verifica-se a redução de eventos adversos e aumento na segurança no uso de medicamentos, o que contribui para a segurança do paciente, para a qualidade do cuidado em saúde, e evita aumento dos custos relacionados a internação (WYMORE et al., 2008; ROTHSCHILD et al., 2010; WEANT et al., 2010; EPPERT; REZNEK, 2011; PROPER et al., 2015; DAVIS et al., 2016, ROMAN et al., 2018).

2.2 PROGRAMAS DE *STEWARDSHIP* ANTIMICROBIANO

Infecções causadas por microorganismos resistentes têm sido reportadas em todo o mundo e estão associadas com piores desfechos clínicos, maior morbidade e mortalidade, além de contribuem para o aumento dos custos dos cuidados em saúde (TRINH; KLINKER, 2015; LOSIER et al., 2017). O aumento da resistência deve-se em parte ao uso abusivo e indevido de antimicrobianos, e é reconhecido como uma crescente ameaça à saúde, já que o surgimento de novos padrões de susceptibilidade ultrapassaram o desenvolvimento de novos antimicrobianos (LOSIER et al., 2017).

Em resposta a esta crescente resistência, o conceito de programa de *Stewardship* antimicrobiano (PSA) foi introduzido por Dale Gerding. Por consenso o programa é definido como: "conjunto de intervenções coordenadas destinadas a melhorar e mensurar o uso apropriado de agentes antimicrobianos, promovendo a seleção do regime ideal destes medicamentos, incluindo dosagem, duração da terapia e via de administração". O programa objetiva, portanto, otimizar a terapia antimicrobiana a fim de aumentar a segurança dos pacientes, minimizar o uso inapropriado dos antimicrobianos, e prevenir o surgimento da resistência dos microorganismos (TRINH; KLINKER, 2015; BARLAM et al., 2016; PARENTE; MORTON, 2018).

Inicialmente os PSA foram implementados nas unidades de internação hospitalar e nas unidades de terapia intensva. A expansão destes programas para outras áreas de cuidado em saúde, como os centros cirúrgicos ambulatoriais, os centros de diálise, as casas de longa permanência e os serviços de emergência é recomendada e vem ocorrendo gradualmente (TRINH; KLINKER, 2015; BARLAM et al., 2016).

Quatro recomendações principais são sugeridas para a implementação e atuação dos PSA, eles compreendem ações de intervenção, de otimização, diagnósticas, e de mensuração dos resultados. Ações de intervenção envolvem a necessidade de pré-autorizações para o uso de antimicrobianos, a revisão prospectiva das prescrições por Médicos Infectologistas ou farmacêuticos e *feedbacks* aos prescritores, a promoção de educação, e o desenvolvimento de protocolos institucionais para o uso de antimicrobianos. Ações de otimização incluem a otimização da terapia com base em princípios farmacocinéticos e farmacodinâmicos, a transição da via endovenosa (EV) para a via oral, a confirmação de alergias a antimicrobianos, e a redução do tempo de terapia. Ações relacionadas ao diagnóstico visam principalmente a aproximação entre o microbiologista e o prescritor, além do uso de testes rápidos. Por fim, a mensuração dos

resultados deve envolver o uso de antimicrobianos na forma de dias de terapia, o custo da terapia, e o impacto das diversas ações no desfecho clínico (BARLAM et al., 2016).

Os benefícios já verificados do PSA incluem melhores desfechos clínicos, redução nos eventos adversos, melhoria nas taxas de suscetibilidade antimicrobiana, e otimização do uso de recursos, com maior adesão a protocolos e menor tempo de tratamento e custo da terapia antimicrobiana (KAKI et al., 2011; OHL; ASHLEY, 2011; WAGNER et al., 2014; BARLAM et al., 2016; LOSIER et al., 2017).

2.2.1 Programas de *Stewardship* Antimicrobiano nos Serviços de Emergência

Infecções estão entre as principais causas de procura por atendimento de emergência. Estas resultam na prescrição de antimicrobianos, porém estima-se que cerca de metade destas prescrições são desnecessárias ou inapropriadas. A incerteza diagnóstica é a principal causa das prescrições desnecessárias. Já a necessidade da tomada de decisão rápida e a falta de informações sobre o histórico dos pacientes contribuem para as prescrições inapropriadas (MAY et al., 2013; DEMONCHY et al., 2014; LOSIER et al., 2017).

O impacto do uso de antimicrobianos nos SE vai muito além destes, já que as prescrições iniciadas nestes serviços rotineiramente são continuadas nas unidades de internação. Portanto, podem influenciar nas tendências de consumo de antimicrobianos e de resistência dos microrganismos na instituição. Desta forma, os SE são um importante alvo para a implementação de estratégias que buscam otimizar o uso destes medicamentos (MAY et al., 2013; PULCINI, 2014; BARLAM et al., 2016; BISHOP, 2016; DUMKOW; BEUSCHEL; BRANDT, 2017).

Algumas características dos SE impõem barreiras para a implementação de PSA nestas unidades, como a grande rotatividade de profissionais e pacientes, a variedade de condições atendidas, a incerteza diagnóstica, e a necessidade da rápida tomada de decisões (MAY et al., 2013). Apesar do reconhecimento e recomendação sobre a necessidade de implementação dos PSA nos SE, este ainda é um tópico negligenciado, e a combinação ideal dos recursos, intervenções e profissionais necessários para promover o uso apropriado de antimicrobianos neste serviço ainda é desconhecida (PULCINI, 2014).

Para o sucesso do programa as intervenções promovidas pelo PSA devem ser customizadas para as necessidades locais, comportamento dos prescritores, barreiras e recursos do SE (BARLAM et al., 2016). É importante considerar que no atendimento de emergência os

antimicrobianos de amplo espectro são muitas vezes os mais apropriados para o tratamento inicial de infecções ameaçadoras da vida, e portanto, garantir o tratamento empírico mais apropriado pode ser o principal foco dos PSA nestes serviços (MAY et al., 2013). Além disso, outras estratégias são citadas como indispensáveis para o sucesso dos PSA no SE, como o envolvimento multiprofissional, respeito a autonomia dos prescritores, integração ao fluxo de trabalho e disponibilidade para consultoria no momento da tomada de decisões (DEMONCHY et al., 2014;TRINH; KLINKER, 2015).

A implementação bem sucedida de intervenções nos SE já foi demonstrada, sendo a promoção de educação, o estabelecimento de protocolos institucionais e os *feedbacks* aos prescritores as estratégias mais descritas (LOSIER et al., 2017). As melhorias observadas envolveram a maior adesão a protocolos institucionais, o aumento da adequação das prescrição de antimicrobianos, a redução no uso de antimicrobianos, e os melhores desfechos clínicos (AKENROYE et al., 2013; JULIÁN-JIMÉNEZ et al., 2013; PERCIVAL et al., 2015).

2.2.2 A participação de farmacêuticos em Programas de *Stewardship* Antimicrobiano nos Serviços de Emergência

O sucesso dos PSAs depende de uma ação coordenada da equipe multiprofissional, já que cada membro tem o conhecimento único de sua expertise, o que fortalece a equipe. A participação dos farmacêuticos nestes programas é recomendada pela Infectious Disease Society of America, que sugere uma atuação de liderança, ao lado do Médico Infectologista (BARLAM et al., 2016).

O conhecimento deste profissional, sua boa interação multidisciplinar, seu envolvimento em comitês hospitalares, além de sua capacidade de assistir a todos os pacientes do serviço, o colocam em uma posição única para promover o uso adequado de antimicrobianos (BISHOP, 2016; PARENTE; MORTON, 2018). A contribuição do farmacêutico para o uso adequado de antimicrobianos ocorre através de diversas iniciativas, que variam de acordo com o nível de cuidado e os recursos disponíveis (BARLAM et al., 2016; LOSIER et al., 2017).

No SE foram relatadas atividades ligadas às quatro principais recomendações de implementação e atuação dos PSA. Dentre elas se destacam: a promoção da educação, o desenvolvimento de *guidelines* e protocolos institucionais, a revisão prospectiva das prescrições, os *feedbacks* aos prescritores, a promoção do escalonamento ou descalonamento do espectro e da descontinuação de terapias, a identificação de cobertura antimicrobiana

duplicada desnecessária, a adequação de doses com base em parâmetros farmacocinéticos e farmacodinâmicos, a promoção da implementação de testes de diagnóstico rápido, e a participação em comitês que avaliam os impactos das ações de PSA (BARLAM et al., 2016; BISHOP, 2016; PARENTE; MORTON, 2018).

Apesar de recente, a contribuição de farmacêuticos aos PSA nos SE já foi capaz de reduzir a duração de tratamento, o custo geral do cuidado, e os erros relacionados ao uso de antimicrobianos (DUNN et al., 2011).

2.3 OTIMIZAÇÃO DE DOSE DE ANTIMICROBIANOS

O uso de doses padronizadas de antimicrobianos pode resultar em concentrações subterapêuticas e falha terapêutica, bem como em concentrações supra terapêuticas, toxicidade e exposição desnecessária aos antimicrobianos. Ambas as situações contribuem para o desenvolvimento de resistência aos antimicrobianos e piores desfechos clínicos (ROBERTS; TACCONE; LIPMAN, 2015). A otimização de doses de antimicrobianos é uma estratégia que busca aprimorar o uso destes fármacos, e assim contribuir para a redução de efeitos adversos e da resistência bacteriana, e também para a manutenção do seu valor terapêutico (ASÍN-PRIETO; RODRÍGUEZ-GASCÓN; ISLA, 2015).

Doses terapêuticas de antimicrobianos, bem como a estimativa de parâmetros farmacocinéticos (PK), são geralmente determinados em voluntários saudáveis. No entanto, o hospedeiro de uma infecção nunca é saudável, mas sim um paciente que apresenta uma situação especial, na qual parâmetros PK, como a depuração renal, o volume de distribuição, e a ligação a proteínas plasmáticas podem estar alterados. Tais alterações podem influenciam na PK de antimicrobianos e por consequente o desfecho da terapia. Além disso, comumente doses terapêuticas não são estimadas considerando o tratamento de microorganismos resistentes. Portanto, alterações nas concentrações inibitórias mínimas de microrganismos resistentes representam uma alteração farmacodinâmica importante, e que pode influenciar na efetividade da terapia (ASÍN-PRIETO; RODRÍGUEZ-GASCÓN; ISLA, 2015; ROBERTS; TACCONE; LIPMAN, 2015).

A análise farmacocinética/farmacodinâmica (PK/PD) integra o conhecimento sobre os mecanismos envolvidos nas mudanças de concentração do antibiótico no organismo do paciente, ao conhecimento sobre os mecanismos envolvidos no efeito dos antimicrobianos junto

aos microrganismos alvo. Ademais, estuda as doses necessárias para aumentar a possibilidade de sucesso terapêutico, bem como para minimizar os efeitos adversos e surgimento de resistência. Desta forma, permite a seleção da dose ideal de cada antimicrobiano, considerando as particularidades do paciente e do processo infeccioso (ASÍN-PRIETO; RODRÍGUEZ-GASCÓN; ISLA, 2015; ROBERTS; TACCONE; LIPMAN, 2015).

A análise PK/PD visando a otimização de dose de antimicrobianos já permitiu o estabelecimento algumas práticas clínicas. Dentre elas o uso de infusões estendidas ou contínuas de beta-lactâmicos, bem como uso de doses de ataque para atingir rapidamente concentrações terapêuticas e posterior dose de manutenção definida a partir da função renal do paciente. Estas estratégias de otimização de dose foram capazes de melhorar taxas de cura clínica, minimizar a resistência antimicrobiana, e evitar a ocorrência de toxicidade (CUNHA; OPAL, 2018).

2.3.1 Otimização de dose de antimicrobianos com base na função renal

A depuração de diversos antimicrobianos, como beta-lactâmicos, glicopeptídeos, aminoglicosídeos dentre outros dependem de uma função renal normal, já que os rins são a principal via de eliminação destes. Alterações da função renal são comuns em pacientes hospedeiros de infecções e acarretam em modificações na PK dos antimicrobianos, já que sua depuração estará alterada (ONUFRAK; FORREST; GONZALEZ, 2016; LASTOURS, 2018).

A funcionalidade renal pode se apresentar aumentada, desta forma maior será a taxa de eliminação de antimicrobianos, e menores as concentrações destes no organismo. Por outro lado, uma função renal diminuída implica em menores taxas de eliminação dos antimicrobianos, e por conseguinte acúmulo e exposição desnecessária a maiores concentrações destes (ASÍN-PRIETO; RODRÍGUEZ-GASCÓN; ISLA, 2015; ONUFRAK; FORREST; GONZALEZ, 2016).

Atenção especial é dirigida a pacientes com função renal reduzida, já que apresentam alto risco de desenvolvimento de toxicidade relacionada a antimicrobianos, o que aumenta a morbidade e mortalidade destes, bem como eleva os custos relacionados ao seu cuidado. Portanto, o ajuste de dose de antimicrobianos em pacientes menor função renal deve ser enfatizado (FAHIMI; EMEMI; FAROKHI, 2012; LASTOURS, 2018).

De modo geral doses de ataque de antimicrobianos devem ser administradas a fim de que concentrações terapêuticas sejam alcançadas em um breve período de tempo. Posteriormente a dose de manutenção deve ser definida com base na função renal do paciente,

já que esta se relaciona bem com a taxa de eliminação de fármacos. Em geral, o ajuste da dose de antimicrobianos é realizado através de redução das doses, aumento do tempo de intervalo entre as doses, ou ambos (CUNHA; OPAL, 2018; LASTOURS, 2018). Não há definição sobre qual profissional deve conduzir o ajuste de dose de antimicrobianos, porém em diversos hospitais o farmacêutico é responsável por esta tarefa (BISHOP, 2016).

2.3.2 O papel do farmacêutico na otimização de dose de antimicrobianos com base na função renal

Farmacêuticos são considerados os principais promotores do uso adequado de antimicrobianos. Acredita-se que este profissional está em uma posição única para promover a otimização de dose de terapias antimicrobianas em acordo com a função renal do paciente, já que possui conhecimento farmacocinético e farmacodinâmico, treinamento clínico, e pode oferecer cuidados a todos os pacientes em sua unidade de atuação (BARLAM et al., 2016; BISHOP, 2016).

Estudos demonstram que a atuação do farmacêutico na promoção do ajuste de dose de antimicrobianos em pacientes com função renal diminuída é necessária. Isto se deve, especialmente, às grandes proporções de prescrições inadequadas encontradas, e aos prejuízos que estas podem provocar nos pacientes (ARRABAL-DURÁN et al., 2014; CABELLO-MURIEL et al., 2014). Ademais, estudos evidenciam que esta atividade do farmacêutico é capaz de reduzir a parcela de antimicrobianos prescritos em sobredose, e portanto aumentar a adequação das prescrições de pacientes com função renal reduzida (BERTSCHE et al., 2009; HASSAN et al., 2009; CABELLO-MURIEL et al., 2014; DEWITT et al., 2016). Finalmente, foi sugerido que a presença do farmacêutico na unidade e sua participação em *rounds* contribui para o aceite das recomendações de ajustes de dose pela equipe Médica e assim para maiores taxas de adequação das prescrições (BERTSCHE et al., 2009; HASSAN et al., 2009).

A orientação do farmacêutico sobre o correto ajuste de dose de antimicrobianos de acordo com a função renal reduzida do paciente contribui para redução dos efeitos adversos, redução dos custos terapêuticos e de internação, bem como redução do tempo de internação e da mortalidade, além de preservar a efetividade terapêutica (JIANG et al., 2014).

2.4 CEFEPIMA

A cefepima é uma cefalosporina de quarta geração, seu mecanismo de ação baseia-se na inibição da síntese da parede celular bacteriana. Possui amplo espectro de ação e tem grande estabilidade à hidrólise por β-lactamases, portanto torna-se bastante útil para o tratamento empírico de infecções graves em pacientes hospitalizados quando desconfia-se de microorganismos gram-positivos, *Enterobacteriaceae* e *Pseudomonas* como agentes etiológicos (HILAL-DANDAN; BRUNTON, 2015).

Este antimicrobiano está disponível para administração por via EV ou intramuscular. De forma geral, a dose recomendada para o adulto varia entre 1 a 2 gramas via EV a cada 8 ou 12 horas, dependendo do provável sítio e gravidade da infecção. Apresenta boas concentrações na urina, bile, vesícula biliar, fluído pustular e na mucosa brônquica, além de ter boa penetração no líquido cerebroespinhal. Seu metabolismo é minimamente hepático, a excreção ocorre quase 100% por via renal, sendo 85% na forma de droga inalterada, portanto as doses devem ser ajustadas para pacientes com insuficiência renal (MAXIPIME, 2013; HILAL-DANDAN; BRUNTON, 2015).

Dentre suas indicações estão o tratamento das infecções intra-abdominais, do trato respiratório, de pele, do trato urinário, e neutropenia febril, além das indicações *off-label*, como meningite, osteomielite e infecções de pé diabético. De maneira geral a duração do tratamento varia entre 7 a 14 dias (BERBARI et al., 2015; HILAL-DANDAN; BRUNTON, 2015; TUNKEL et al., 2017).

Alguns eventos adversos foram reportados para este fármaco, como: reação de Coombs positiva, flebite, dor de cabeça, prurido, diarréia, náuseas, vômito, eosinofilia e febre, depressão da medula óssea e granulocitopenia, hipersensibilidade, e sintomas neurológicos (encefalopatia, afasia, mioclonia, convulsões e status epilepticus não convulsivo) (MAXIPIME, 2013; HILAL-DANDAN; BRUNTON, 2015).

2.4.1 Neurotoxicidade induzida por cefepima

Eventos adversos relacionados ao SNC, como a encefalopatia (*delirium*, confusão, coma), convulsões e status epilepticus não convulsivo, são reportados para as cefalosporinas, porém há evidências que a cefepima apresenta maior risco para a ocorrência destes (TANAKA

et al., 2013). Acredita-se que a fisiopatologia da neurotoxicidade causada pela cefepima está relacionada a inibição de receptores do ácido γ -aminobutírico (GABA), a qual se dá de maneira concentração-dependente (GRILL; MAGANTI, 2008).

A incidência idiopática de neurotoxicidade em pacientes em tratamento com cefepima foi estimada em cerca de 3% (GRILL; MAGANTI, 2011). Porém para pacientes com insuficiência renal tal incidência pode chegar a 15%. Casos reportados na literatura ocorreram majoritariamente em paciente com insuficiência renal (FUGATE et al., 2013; APPA et al., 2017). Tendo em vista que 85% da droga é eliminada em sua forma inalterada pelos rins, quando há disfunção renal a meia vida deste antimicrobiano pode aumentar de 2 para até 13 horas (MAXIPIME, 2013). Como resultado haverá elevação das concentrações séricas de cefepima, e portanto maior a fração livre da droga disponível para penetrar no SNC e possivelmente causar neurotoxicidade (GRILL; MAGANTI, 2008). Assim, torna-se necessário o ajuste de dose nestes pacientes (US FOOD AND DRUG ADMINISTRATION, 2012; MAXIPIME, 2013). Já houveram relatos de neurotoxicidade em pacientes com insuficiência renal tratados com doses ajustadas de cefepima, porém estes são mais raros (GANGIREDDY; MITCHELL; COLEMAN, 2011; ISITAN; FERREE; HOHLER, 2017).

Além da insuficiência renal outros fatores são apontados como contribuintes para a ocorrência de neurotoxicidade quando em tratamento com cefepima, como idade avançada, distúrbios neurológicos pré-existentes e uso de doses excessivas (MATTAPPALIL; MERGENHAGEN, 2014; APPA et al., 2017; PAYNE et al., 2017).

O tempo médio entre o início do tratamento com cefepima e a ocorrência dos primeiros sintomas é de 4 dias. Os principais sintomas reportados são rebaixamento do nível de consciência (47 a 80%), mioclonus (40 a 42%), confusão (42%), afasia (9 a 15%), convulsões (11 a 13%), status epilepticus não convulsivo (31%), agitação e desorientação (11% a 47%). A média de tempo entre os sintomas iniciais e o diagnóstico de neurotoxicidade é de 5 dias, isso pode ser devido ao fato de que os sintomas muitas vezes mimetizam o *delirium* ou a encefalopatia decorrente de outras causas. A realização de eletroencefalograma auxilia no diagnóstico, estima-se que em 81% dos casos diagnosticados este exame é realizado, sendo a ocorrência de ondas trifásicas indicativas de encefalopatia metabólica tóxica o padrão reportado mais frequentemente (APPA et al., 2017; PAYNE et al., 2017).

As medidas para reversão da neurotoxicidade incluem interrupção do tratamento, redução da dose, uso de uma ou mais drogas anticonvulsivantes, e realização de hemodiálise. A resolução dos sintomas ocorre em média 2 dias após a instituição de medidas, sendo este

tempo inferior quando a medida instituída foi a hemodiálise. Considera-se o reconhecimento rápido da neurotoxicidade induzida por cefepima fundamental, pois somente a adoção de medidas permite a reversão completa do quadro e previne maior morbidade e mortalidade (APPA et al., 2017; PAYNE et al., 2017).

A ocorrência de neurotoxicidade e convulsões em decorrência do mau ajuste da cefepima de acordo com a função renal já foi estudada em unidades de internação e em unidades de terapia intensiva, porém estudos semelhantes em SE não estão disponíveis (FUGATE et al., 2013).

3. OBJETIVOS

3.1 GERAL

- Verificar a adequação de dose da terapia antimicrobiana com cefepima em pacientes com insuficiência renal admitidos a EMA-HCPA.

3.2 ESPECÍFICOS

- Quantificar as recomendações realizadas a fim de promover o ajuste de dose de cefepima para a função renal dos pacientes e verificar as origens destas;
- Quantificar os ajustes de dose de cefepima para a função renal dos pacientes realizados pela equipe médica, e verificar se foram decorrentes ou não de recomendações;
- Quantificar relatos de ocorrência de neurotoxicidade nos pacientes que iniciaram terapia antimicrobiana com cefepima na EMA-HCPA;
- Verificar possibilidades de melhoria da atuação do farmacêutico na promoção de ajustes de dose da terapia antimicrobiana com cefepima.

4. ARTIGO CIENTÍFICO

As sessões “MÉTODOS”, “RESULTADOS” e “DISCUSSÃO” apresentam-se na forma de manuscrito elaborado em acordo com as normas exigidas pelo periódico *International Journal of Pharmacy Practice* para *original research papers.*

APPROPRIATENESS OF CEFEPIME DOSING IN PATIENTS WITH RENAL INSUFFICIENCY IN THE EMERGENCY DEPARTMENT OF AN ACADEMIC HOSPITAL: A CROSS-SECTIONAL STUDY

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ABSTRACT

Objectives

Cefepime is a broad-spectrum antibiotic commonly prescribed for the treatment of nosocomial infections. Neurotoxic effects of cefepime are often reported and renal insufficiency is suggested as its major risk factor, especially when inappropriately adjusted or large doses are administered. Therefore, efforts to promote proper cefepime dosing in patients with renal insufficiency should be emphasized. The aim of this study was to verify appropriateness of cefepime dosing in patients with renal insufficiency admitted to an Emergency Department.

Methods

This was a retrospective cross-sectional study of patients admitted to the emergency department of an academic hospital who had a cefepime prescription for the treatment of an infection. For patients with renal insufficiency, cefepime dosing appropriateness was evaluated.

For those with inappropriate cefepime dosing a search was made to find if recommendations regarding dosing adjustment had been made. Descriptions of neurological symptoms that could indicate cefepime-induced neurotoxicity were searched on health records of all included patients.

Key Findings

Of the 205 patients receiving cefepime treatment, 69 had renal insufficiency. Of these, 75.4% had cefepime dosing inappropriately adjusted for the reduced renal function. Recommendations on dosing adjustment were made by Pharmacists and infection disease Physicians, in addition prescribers made dosing adjustments regardless of recommendations. After cefepime dosing adjustments, the proportion of patients with renal insufficiency which had cefepime dosing correctly adjusted increased from 24.6% to 69.6%. Neurological symptoms were reported frequently, however, only 6 cases were considered as cefepime-induced neurotoxicity.

Conclusions

Inappropriate cefepime dosing was frequent within patients with renal insufficiency admitted to the ED. Multi-professional work contributed to promoting proper cefepime dosing. Additional strategies should be adopted to ensure proper cefepime dosing to all patients and to avoid cefepime induced neurotoxicity.

KEYWORDS

Cefepime; Emergency Department; Renal Insufficiency; Dosing Adjustment; Multi-professional.

WORD COUNT

2990 words.

INTRODUCTION

Due to the worldwide increase in bacteria resistance, broad-spectrum antibiotics are increasingly needed for the treatment of infections [1]. Cefepime is one of these antibiotics. It is a fourth-generation cephalosporin commonly prescribed empirically for the treatment of nosocomial infections including respiratory tract infections, urinary tract infections, skin and soft tissue infections, and others [2,3]. One of the complications associated with cefepime use is the occurrence of neurotoxicity, characterized by neurological symptoms that include confusion, reduced consciousness, myoclonus and seizures [4,5]. It is suggested that the mechanism of cefepime toxicity is related to its accumulation in the cerebrospinal fluid and inhibition of the γ-aminobutyric acid (GABA) receptors [6].

Cefepime elimination is mainly determined by the kidneys, 85% of the administered dose is eliminated unchanged through this route [3]. Patients with renal insufficiency commonly show changes in pharmacokinetic parameters, especially on clearance. Thereby, a decrease in renal function induces a reduction in total clearance of cefepime. It leads to cefepime accumulation and results in serum and cerebrospinal fluid supratherapeutic levels. As a consequence neurological symptoms may develop and the patient's morbidity can be increased [6]. Previous studies suggest renal insufficiency as the major risk factor for cefepime neurotoxicity, especially when inappropriately adjusted or large doses are administered [4,5].

The frequency of patients with renal insufficiency is increasing with the ageing of the population. Patients with renal insufficiency are hospitalized more frequently than those with a normal renal function. Thus, renal insufficiency in hospitalised patients is common [7, 8]. Studies show that prescription of inadequate doses of cefepime are common within this population [9,10]. Therefore, efforts to promote proper cefepime dosing or proper dose adjustment in patients with renal insufficiency should be emphasized. Whereas this can minimize toxicity, decrease the workload for nurses and the costs [11].

Antibiotic stewardship programs are designed to improve the appropriate use of antibiotics, reduce adverse events, and minimize rates of bacterial resistance. These programs include strategies to support antibiotic dose optimization based on patient and disease characteristics. Thus, efforts to promote proper cefepime dosing or dose adjustment in patients with renal insufficiency are included in the antibiotic stewardship programs. The Infectious Disease Society of America emphasizes the importance of infectious disease Physicians and Pharmacist leadership for the success of antibiotics Stewardship interventions [1].

The appropriate use of antibiotics must be made in all hospital settings. It is suggested that special attention should be given to the emergency department (ED). Overcrowding, diagnostic uncertainty and lack of knowledge about patients medical history are common in this setting and can lead to inadequate antibiotic prescriptions [1, 12-14]. Furthermore, antibiotic prescriptions initiated in this department tend to be continued in other hospital units and can influence the use of antibiotics in the whole institution [15].

Studies evaluating cefepime dosing appropriateness in patients with renal insufficiency in the ED are scarce in the published literature and evaluate very small samples that are not representative. Given the importance of this subject and the benefits that it can bring to the patient, the aim of this study was to verify cefepime dosing appropriateness in patients with renal insufficiency admitted to an ED.

METHODS

Study design and setting

A retrospective cross-sectional study was conducted in the ED of an academic hospital in Brazil. The ED has 41 adult beds distributed in 3 sections according to the patient's gravity and is usually overcrowded. The unit is primarily concerned with the treatment of patients with life-threatening conditions like stroke, heart attack and sepsis, and also chronic conditions such as cancer and post-transplant patients. Physicians work in shifts and medical residents from all major fields rotate through the ED. A Pharmacist or a pharmacy resident is present in the ED from 7:00 to 18:00, Monday to Friday.

The Pharmacist's role in this ED includes evaluation of every patient's prescription considering their clinical condition, and as needed to make recommendations related to medicine therapies to Physicians. Recommendations can be made by using an electronic form that includes an alert in the patient's prescription, or by direct communication with the Physician.

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre.

Patient selection

Male and female patients over 18 years of age admitted to the ED between April 1, 2017, and August 31, 2017, with a cefepime prescription were eligible for inclusion. Patients on

dialysis, pregnant, who received cefepime for less than 48 hours, or had relevant data for the study missing were excluded.

Patients were identified through a report that listed all those with a cefepime prescription during the considered period. Patients were randomly selected for inclusion.

Outcomes

The primary outcome was the frequency of cefepime dosing appropriateness in patients with renal insufficiency. Secondary outcomes included the Pharmacists and infection disease Physicians from the infection control committee recommendations to promote proper cefepime dosing, the acceptance of these recommendations by prescribers, and the occurrence of cefepime-induced neurotoxicity.

Study variables and data collection

Demographic and clinical data were obtained from AGHUse, an electronic system developed in the hospital which integrates exams results, prescriptions and health records. Age, sex and race were recorded for each patient. Regarding cefepime therapy, the data recorded included therapy indication, dose and frequency (dosage) prescribed by the Physician.

Patients renal function was obtained by estimating glomerular filtration rate through the CKD-EPI Creatinine Equation. AGHUse automatically calculates the estimated glomerular filtration rate (eGFR) using the last creatinine measurement and shows it in prescriptions. The eGFR considered for this study was the one obtained from exams performed the day after the beginning of cefepime therapy, if eGFR was not available at this point of therapy, the latest one was considered (if obtained up to 7 days before).

Patients with eGFR below 60 mL/min/1.73m² were considered as having renal insufficiency. Recommendations in databases and in cefepime label use this eGFR value as the cut-off to adjustments. Accordingly, for these patients, cefepime dosing appropriateness was evaluated. To determine the appropriateness, therapeutic indication, dosage and eGFR were analysed and compared with recommendations on databases and in cefepime label. Prescriptions were considered appropriate or inappropriate. Database considered were UpToDate® and Micromedex® [16, 17].

For patients with cefepime dosing considered as inappropriate, a search was performed to find if recommendations suggesting dose adjustment had been made, and also if these were accepted by the prescribers. Recommendations on dosing adjustment were obtained from the

pharmacy service records or from antibiotics pre-authorization forms. Prescribers acceptance was inferred from changes in prescription.

Descriptions of neurological symptoms that could indicate neurotoxicity, like confusion, changes in mental status, myoclonias and seizure activity during cefepime therapy were searched on all included patients health records. For those with reported neurological symptoms, a search was made to find information about the prior existence of neurological diseases, and to find if electroencephalogram had been performed.

Sample and data analysis

The estimated sample size of 158 patients was calculated using WinPepi, version 11.65, based on a confidence rate of 95%, a margin of error of 5% and a proportion of 15%, as referred by Dewitt *et al.* [9]. Data was systematised and analysed using PASW Statistics for Windows, version 18.0. Descriptive methods were used. Discrete variables were expressed as counts and percentages. Continuous variables were expressed as the mean ± SD.

RESULTS

During the 5-month study period, 751 patients admitted to the ED had a cefepime prescription. Of 300 randomly selected patients considered for inclusion 95 were excluded based on exclusion criteria. A total of 205 patients met the inclusion criteria (Figure 1).

There were a total of 115 males and 90 females. 85.9 % were white and 14.1% were blacks. Mean age was 61.6 ± 16.6 years. Mean eGFR was 75.9 ± 32.6 mL/min/1.73m^3. The predominant diagnosis was respiratory tract infection (54.6%), followed by intra-abdominal infection (11.2%), and neutropenic fever (10.2%). The most frequent dosages were 2g three times a day (57.1%), 2g twice daily (21%), and 1g three times a day (16.1%) (Table 1).

Of the 205 included patients, 69 (33.7%) had an eGFR below 60 mL/min/1.73m^2. In 52 (75.4%) of them, cefepime dosing was inappropriate for the reduced renal function (Table 2). Pharmacists made recommendations for dose adjustments in 7 patients with inappropriate cefepime dosing, of which 6 were accepted by prescribers. Other 7 recommendations had been made by an infection disease Physician of the infection control committee, all of them were accepted by prescribers. 38 patients had no adjustment recommendation provided. Despite this, prescribers adjusted the dose of 18 patients. Thus, after cefepime dosing adjustments, the proportion of patients with renal insufficiency which had cefepime dosing correctly adjusted increased from 24.6% to 69.6%.

Neurological symptoms (confusion, reduced consciousness, agitation, disorientation, delirium and myoclonus) were reported in 28 (20.6%) patients with normal renal function. However, only 4 (2.9%) cases were considered as cefepime-induced neurotoxicity. Described symptoms were confusion, delirium and myoclonus. All they were older than 70 years and one had previous dementia. Otherwise, in patients with renal insufficiency neurological symptoms were reported in 20 (29%) of them. Nevertheless, only 2 (2.9%) cases were considered as cefepime-induced neurotoxicity. Described symptoms were confusion and delirium. Both had cefepime dosing properly adjusted to decreased renal function. Only one of them was over 70 years old. Electroencephalogram was not performed in any patient with neurological symptoms, regardless of the symptoms cause was considered as cefepime-induced or not.

DISCUSSION

In this retrospective, cross-sectional, single-centre study of ED patients in treatment with cefepime, renal insufficiency was common. Inappropriate cefepime dosing in these patients was frequent either. It was found that multi-professional efforts to promote appropriate cefepime dosing adjustments for renal function were made. Despite these, some doses remained inadequate. Neurological symptoms were common, however, few were considered as cefepime-induced.

This study had some limitations. It was a retrospective study, therefore data collected was limited to information recorded in the health records which can be inaccurate or incomplete. During the study period, not all Pharmacists recommendations were recorded in the AGHUse electronic system or in digital files, also Pharmacists work overload due to overcrowding can have contributed to registry failures. This can have limited data collection and underestimated the actual rate of recommendations on cefepime dosing adjustment made by Pharmacists.

Only one study evaluating the appropriateness of cefepime dosing in patients with renal insufficiency in ED have been found. However, this study evaluated a small sample in an institution which had a renal dosing protocol that allows Pharmacists to adjust the dosage and frequency of several medications, including cefepime [9]. It may have limited the discussion of this study results, since it had to be done by comparison with previous studies that evaluated other antibiotics and even other drugs, and in several hospital units.

It was a single-centre study, therefore results may not be generalizable to other ED or institutions. In the same way, the study was designed to analyse only cefepime, and so results may not represent other antibiotics.

The predominance of the 2g three times a day dosage could be seen as the use of a standard dosage. However, if it is observed that the two main indications for cefepime therapy were respiratory tract infection and febrile neutropenia, which together correspond to nearly 65%, this dosage choice is reasonable. Since it is the recommended dosage to treat these conditions by cefepime label as well as by the databases searched [3, 16, 17].

Renal insufficiency in hospitalised patients is common, and its frequency depends on the setting [8]. A high proportion of renal insufficiency is expected in critically ill patients due to its particular pathophysiological situation [18]. The frequency of renal insufficiency found in the present study was almost 35%. This may be because the patients admitted to the ED studied usually are in a critical health condition, have poor access to primary health care, significant comorbidities, and have undergone several hospitalizations and procedures.

Inappropriate cefepime dosing in patients with renal insufficiency was frequent in the present study, i.e., about 75%. It agrees with prior studies conducted in diverse hospital settings and that included even other antibiotics and medicines classes, which have observed that inappropriate dosing in patients with renal impairment is common. Sweileh *et al* [19] observed that 73% of all medicines analysed were prescribed in doses inappropriate to renal impairment. Prajapati & Ganguly [20] found 80% of antibiotics prescriptions to be improper for decreased renal function. Although Dewitt *et al.* [9] evaluated cefepime dosing in patients with renal insufficiency in ED, the inadequacy frequency was much lower (33%), this is because the study was conducted in an institution that had a renal dosing protocol which allows Pharmacists to adjust cefepime doses.

The high percentage of inappropriate doses found can be due to the lack of prescribers experience, since many are training Physicians who may not be familiar with all drug's characteristics. Furthermore, many patients are admitted with septic shock to the ED. In this condition, prescribers may prefer to maintain higher doses for up to 48 hours due to pharmacokinetic changes [21]. As the adequacy analysis was made considering data from 24 hours after the start of treatment this may have driven the high inappropriateness proportion found. Another explanation for the high frequency of inappropriate doses is the setting characteristics. The lack of complete patient information and the diagnostic uncertainty in combination with the discontinuity in care and intense pressure, frequent situations in the ED, can lead to the overlook of dosing adjustment.

Studies evaluating the adequacy of antibiotic doses in patients with renal insufficiency usually evaluate efforts of only one professional or of computerized dosing programs in dose

optimization. Hassan et al. [22] and Bertsche et al. [18] found that Pharmacists participation in ward rounds to make recommendations on dosing adjustment in renal insufficiency was able to reduce inappropriate dosing in about 50%. Diaz et al. [23] found that a computer-based, semi-automated drug-dosage program was able to increase the percentage of appropriate orders to renal insufficiency from 65% to 86%. In this study, together, Pharmacists, infection disease Physicians from the infection control committee and prescribers promoted dosing adjustments, allowing the cefepime dosing appropriateness rate for renal insufficiency to almost triplicate. It demonstrates that multi-professional effort is critical to the success of dose optimization actions, as suggested previously [1].

Quite troubling was the fact that 20 out of 52 patients with inadequate cefepime dosing to decreased renal function did not receive any consideration for dose optimization. It evidences that additional strategies should be adopted to assist Physicians in cefepime dosing adjustment, so all patients with renal insufficiency receiving inadequate doses get adjustment recommendations. Also, it represents a great opportunity for Pharmacists action through activities of antibiotic stewardship, as previously suggested [24]. The development of an institutional dosing guide by collaboration between infection disease Physicians and Pharmacists to support dose adjustments and provide consensus for dosage recommendations of different databases, the implementations of a monitoring program led by Pharmacists to ensure appropriate doses for patients with renal impairment, and the information technology support to implement alerts and tools in the prescription system are suggested strategies that can be helpful in cefepime dosing optimization [8, 9, 13, 22].

Cefepime-induced neurotoxicity reportedly occurs in 3% of patients in therapy with this medicine. It happens more frequently in patients with renal insufficiency, i.e., 15%, especially when cefepime dose is not adjusted for renal function, even though it can still occur despite those modifications [10, 25, 26]. In this study descriptions of neurological symptoms were found in 28 patients with normal renal function and in 20 with renal insufficiency. Overall, only 6 cases, about 3%, were considered as cefepime neurotoxicity by the medical team, what agrees with the previous incidence rate found. Five out of 6 patients also had other conditions indicated as risk factors for cefepime neurotoxicity, advanced age and previous dementia, what can have contributed to the occurrence of the neurological symptoms observed [27].

The low neurotoxicity rate found can represent a real small incidence as a result of multi-professional efforts to promote dosing adjustment, reaffirming that dose adjustment is critical to minimize the risk of cefepime neurotoxicity. Otherwise, it can represent that cefepime is not

being recognized as the neurological symptoms' cause, this is because Physicians are not aware of cefepime characteristics and toxicity, and also because recognizing cefepime as the neurotoxicity cause is challenging, since symptoms mimic those of delirium and other causes encephalopathy [28]. Therefore, it is necessary to promote education so that Physicians are aware of cefepime characteristics in order to consider its toxicity in all patients experiencing neurological deterioration.

Although it is not a specific test, electroencephalogram is considered as an important tool which aids in the diagnosis of cefepime neurotoxicity that should be commonly used. A recent review found that in up to 81% of cefepime-induced neurotoxicity published case reports electroencephalogram was performed to aid diagnosis [5]. In the present study electroencephalogram was not performed in any patient presenting neurological symptoms. It may have underestimated the number of neurotoxicity cases considered as cefepime-induced by Physicians.

CONCLUSIONS

Inappropriate cefepime dosing was frequent within patients with renal insufficiency admitted to the ED. Multi-professional work contributed to promoting cefepime dose adjustments. These efforts have to be strengthened, as they can prevent cefepime-induced neurotoxicity. Also, more strategies should be adopted in this ED and perhaps in the institution in general, so that all patients receive the appropriate cefepime dosing. The development of an institutional cefepime dosing guide for decreased renal function, the implementation of a monitoring program led by Pharmacists for patients with renal insufficiency receiving cefepime, and the inclusion of alerts in the prescription, are strategies that could be adopted. For this to happen, further studies are required to verify if these strategies are needed for other antibiotics and other hospital units as well, and also if they are feasible to be developed and applicable to the institution routine. Some cases of cefepime neurotoxicity happened, these appear to have been underestimated. To avoid overlook of cefepime-induced neurotoxicity occurrence, strategies to improve its diagnosis should be studied.

DECLARATIONS

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Authors' contributions

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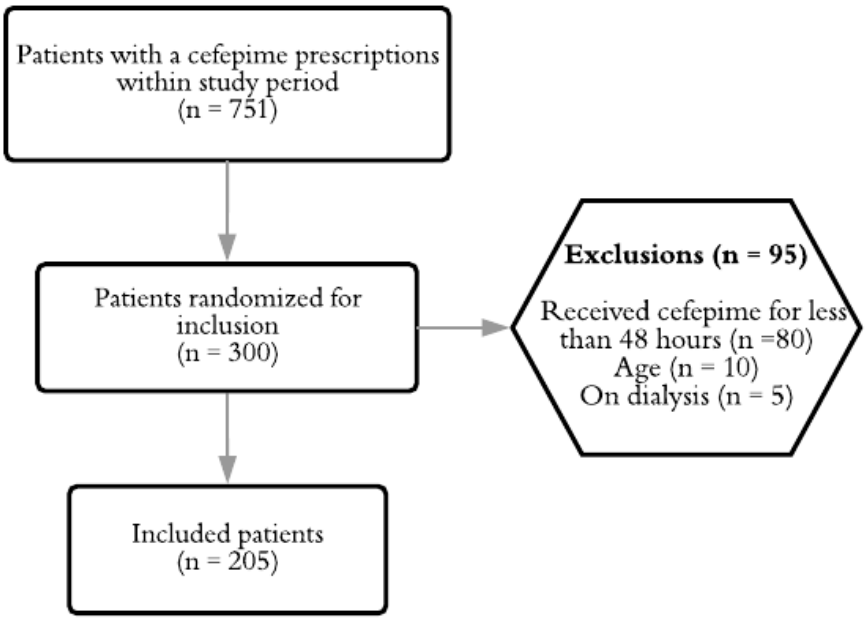

Figure 1. Study flow chart

Selection and inclusion flow of patients in the study from those admitted to the emergency department during the study period and who were treated with cefepime, as well as reasons for patients exclusion.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	**n = 205**
Age (years), mean ± SD	61.6 ± 16.6
Sex, n (%)	
Male	115 (56.1)
Female	90 (43.9)
eGFR (mL/min/1.73m²), mean ± SD	75.9 ± 32.6
Race, n (%)	
White	176 (85.9)
Black	29 (14.1)
Diagnosis, n (%)	
Respiratory	112 (54.6)
Urinary	18 (8.8)
Intra-abdominal	23 (11.2)
Skin and soft tissue	18 (8.8)
Osteomyelitis	3 (1.5)
Neutropenic fever	21 (10.2)
Central nervous system	1 (0.5)
Undifferentiated infection	9 (4.4)
Dosage, n (%)	
1g QD	3 (1.5)
2g QD	1 (0.5)
1g BID	7 (3.4)
2g BID	43 (21.0)
1g TID	34 (16.6)
2g TID	117 (57.1)

Descriptive analysis of patients demographic and clinical characteristics. Discrete variables are expressed as counts and percentages. Continuous variables are expressed as the mean ± SD. eGFR, estimated glomerular filtration rate; QD, once daily; BID, twice daily; TID, three times a day.

Table 2. Cefepime Dosing Appropriateness in Patients with Renal Insufficiency

eGFR < 60 mL/min/1.73m²	**n = 69**
Appropriate for renal function, n (%)	
Yes	17 (24.6)
No	52 (75.4)

Cefepime dosing appropriateness was determined by therapeutic indication, dosage and eGFR analysis and comparison with recommendations on databases. Prescriptions were considered appropriate or inappropriate. Data are expressed as counts and percentages. eGFR, estimated glomerular filtration rate.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	**1**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**19**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**19,20**
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	**21,22**
Objectives	3	State specific objectives, including any prespecified hypotheses	**22**
Methods			
Study design	4	Present key elements of study design early in the paper	**22**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**22**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	**22,23**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**23**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**23,24**
Bias	9	Describe any efforts to address potential sources of bias	**n/a**
Study size	10	Explain how the study size was arrived at	**24**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**24**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**24**
		(*b*) Describe any methods used to examine subgroups and interactions	**n/a**
		(*c*) Explain how missing data were addressed	**n/a**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	**n/a**
		(*e*) Describe any sensitivity analyses	**n/a**
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**24**
		(b) Give reasons for non-participation at each stage	**32** (Figure 1)
		(c) Consider use of a flow diagram	**32** (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**22,33** (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	**n/a**
Outcome data	15*	Report numbers of outcome events or summary measures	**24,25**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**n/a**
		(*b*) Report category boundaries when continuous variables were categorized	**n/a**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**n/a**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**n/a**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**25**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**25**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**26-28**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**25**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**29**

***Give information separately for exposed and unexposed groups.**

5. CONSIDERAÇÕES FINAIS

Doses inadequadas de cefepima em pacientes com insuficiência renal admitidos a EMA-HCPA foram frequentes. Recomendações feitas por farmacêuticos e por médicos infectologistas do Comitê de Controle de Infecção Hospitalar a fim de promover ajustes destas doses foram efetivas. Desta forma, ações multiprofissionais devem ser fortalecidas, já que podem prevenir a ocorrência de neurotoxicidade induzida por cefepima, e assim contribuir para o melhor cuidado do paciente, além de evitar que ocorra acréscimo à carga de trabalho da equipe de enfermagem e aos custos da internação.

Alguns casos de neurotoxicidade decorrente do uso de cefepima foram verificados, porém, estes casos parecem estar subestimados. Ações que busquem melhorar a conscientização sobre a neurotoxicidade induzida por cefepima e aprimorar seu diagnóstico, a fim de evitar que estes casos passem despercebidos, devem ser estudadas e implementadas, visto que o diagnóstico permite a tomada de medidas para o tratamento dos sintomas neurológicos, e portanto melhora o cuidado do paciente.

Apesar de efetivas, as ações multiprofissionais verificadas neste estudo não foram capazes de atingir todos os pacientes com insuficiência renal que estavam recebendo doses inadequadas de cefepima. Isto representa uma grande oportunidade para a atuação farmacêutica na promoção de ajustes de dose ainda no princípio do tratamento. Além disso, indica que estratégias adicionais para tornar a promoção de ajustes de dose mais eficaz devem ser adotadas na EMA-HCPA, como: o desenvolvimento de um guia de ajuste de dose para a função renal através da colaboração entre Médicos Infectologistas e farmacêuticos, a implementação de um programa conduzido por farmacêuticos de monitoramento para pacientes com insuficiência renal em uso de cefepima, e a inclusão de alertas na prescrição sobre a necessidade de ajuste da dose em acordo com a função renal do paciente.

Estudos adicionais, envolvendo outras unidades hospitalares, bem como outros antibióticos são necessários a fim de verificar quais estratégias são mais relevantes, quais podem ser desenvolvidas e se serão aplicáveis a rotina do HCPA.

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ANEXO A - Normas da Revista

Edited By: Christine Bond, University of Aberdeen, UK

Online ISSN:2042-7174

Author Guidelines

Manuscript Preparation

General guidelines

- All contributing authors of a manuscript should include their full name, affiliation, postal address, telephone and email address on the title page of the manuscript. A brief description of contributions should also be listed per author. Anyone who has contributed to the manuscript but does not qualify as an author should appear as an acknowledgement on the title page. One author should be identified as the corresponding author.
- For all manuscripts non-discriminatory (inclusive) language should be used.
- Authors are urged to be succinct, to use the minimum number of tables and figures necessary and to avoid repetition of information between these two media. Given the competition for space within the journal, the length of submission in relation to its likely contribution will be taken into account with regard to acceptability. Guidelines on length are provided below.
- The pages and lines of the manuscript must be numbered.
- The word count (excluding references and the word count of the abstract) should be included on the title page of the manuscript.

Ethical guidelines

- Authors should supply a conflict of interest statement with their submitted manuscript, detailing any financial or personal relationships that may bias their work, or a declaration that they have no conflicts of interest to disclose.
- Original research studies involving animals or human volunteers must include details of ethical approval. This should include:
- (a) the name of the Institutional Review Board or Ethics Committee that approved the study and all protocols
- (b) the date of this approval and
- (c) the number of the certification or document which verified approval of the study.

- If you have not needed to seek ethical approval for the work, we also require the reason for this. Papers that do not comply with internationally accepted ethical criteria will not be accepted for publication.
- Identifying details of patients and study participants should be omitted. If identifying information is essential for scientific purposes, or if there is any doubt about the adequacy of the anonymity protection used, the patient (or parent/guardian) must give written

informed consent for publication. Authors should provide this statement of informed consent upon submission of the manuscript.

- Authors are requested to follow standard reporting guidelines when reporting their studies. For example manuscripts reporting randomised controlled trials must be written in accordance with the CONSORT Statement, and systematic reviews must written in accordance with the PRISMA guidelines. Guidelines for other study designs can be found on the EQUATOR network (http://www.equator-network.org/). Please complete and submit checklists and flow charts together with your articles. Checklists should be submitted as a supplementary file, and flowcharts as a figure.

Further information can be found in our Ethical Guidelines document.

This journal is a member of, and subscribes to the principles of, the Committee on Publication Ethics (COPE).

Language

Manuscripts are accepted only in English (British English). Authors whose first language is not English are recommended to ask a native speaker to proofread their manuscript before submission. Alternatively, a pre-acceptance Editing Service (comprising English language editing, translation services, manuscript formatting and figure preparation) is available and can provide you with expert help to ensure your manuscript is ready for submission. All services are paid for and arranged by the Author, and use of one of these services does not guarantee acceptance or preference for publication.

Original research papers

Original research papers should not exceed 3000 words. Manuscripts should be written in the passive voice.

Abstract

- Structured abstracts are required for all papers and should include objectives, methods, key findings and conclusions.
- Approximate length: 250 words

Keywords

No more than 5 keywords should be supplied for all papers.

Introduction

- An introduction should provide a background to the study (appropriate for an international audience) and should clearly state the specific aims of the study. Please ensure that any abbreviations and all symbols used in equations are fully defined.
- Approximate length: 500-1000 words

Methods

- This section should describe the materials and methods used in sufficient detail to allow the study to be replicated. Please include details of ethical approval in this section.
- Approximate length: 500 - 1000 words

Results

- This section should provide detailed response rates. It is essential to include statistical analyses or other indicators to enable assessment of the variance of replicates of the experiments. Data should not be repeated in figures and tables.
- Approximate length: 700 - 1000 words

Discussion

- The discussion should start with a short sharp paragraph summarising the main findings of the study.
- Followed by a critique of the strengths and limitations of the research.
- The full results should then be discussed in the context of international published literature and the contribution made to the field.
- Any policy, practice and research implications (if any) should be included.
- Approximate length: 700 - 1000 words

Conclusions

- A brief conclusions section should summarise the salient findings of the study. Authors are strongly advised to emphasise the contribution made to the field by their study in this section.
- Approximate length: 150 - 250 words

Tables

- Please keep the number of tables to a minimum.
- Tables should be numbered consecutively (Table 1, Table 2 etc) and each table must start on a separate page at the end of the manuscript.
- Each table must have a title. Each table legend, in paragraph form, should briefly describe the content and define any abbreviations used. If values are cited in a table, the unit of measurement must be stated.
- Tables should not be ruled.

Figures

- Please keep the number of figures to a minimum.
- Each figure must have a title. Each figure legend, in paragraph form, should briefly describe the content and define any abbreviations used. If values are cited in a figure, the unit of measurement must be stated. Graphs must have clearly labelled axes. A key may be included if appropriate.
- It is in the author's interest to provide the highest quality figure format possible. Please be sure that all imported scanned material is scanned at the appropriate resolution: 1200 dpi for line art, 600 dpi for grayscale and 300 dpi for colour.
- Files should be saved as one of the following formats: TIFF (tagged image file format), PostScript or EPS (encapsulated PostScript), and should contain all the necessary font information and the source file of the application (e.g. CorelDraw/Mac, CorelDraw/PC).
- Figures must be saved separate to text. Please do not embed figures in the paper file. The manuscript should indicate the position of the figures (e.g. see Figure 1) and all figures should be numbered consecutively in the order in which they appear in the paper. In multi-part figures, each part should be labelled (e.g. Figure 1(a), Figure 1(b)). The filename for a graphic should be descriptive of the graphic, e.g. Figure1, Figure2a.

- There are a limited number of colour pages within the journal's annual page allowance. Authors should restrict their use of colour to situations where it is necessary on scientific, and not merely cosmetic, grounds. Authors of accepted papers who propose publishing figures in colour in the print version should consult the Production Editor at proof stage to agree on an appropriate number of colour pages. The decision of the Publisher is final.

Authors, Acknowledgements and Funding

- Funding acknowledgements should be written in the following form: "This work was supported by the Medical Research Council [grant number xxx]"
- If the research has not been funded by any specific project grant, please include the statement: "This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors"
- Authors must adhere to the ICMJE definition of authorship http://www.icmje.org/ethical_1author.html and include on the Title Page a brief description of all contributions to the manuscript. Authors of research papers should state whether they had complete access to the study data that support the publication. Please note: Contributors who do not qualify as authors should also be listed and their particular contribution described. This information should appear as an acknowledgement on the Title Page.

References

- References in the text are cited sequentially by number. All citations in the text must appear in the reference list and vice versa. The only exceptions to this are manuscripts not yet in press or published online, papers reported at meetings, or personal communications – these should be cited only in the text, not as a formal reference. Authors should get permission from the source to cite personal communications or unpublished work.
- At the end of the manuscript, references should be listed in numerical order as they appear in the text. Serial titles should be abbreviated in accordance with the standard approved abbreviations used by PubMed or BIOSIS. One-word titles are never abbreviated. Article identifiers, such as the Digital Object Identifier (DOI) or PubMed Unique Identifier (PMID), may be included as appropriate. State the references according to the format of the following examples:

Journal references

Authors are required to archive any web references before citing them using WebCite ® technology (http://www.webcitation.org). This is an entirely free service that ensures that cited webmaterial will remain available to readers in the future.

One author:

Szeto HH. Simultaneous determination of meperidine and normeperidine in biofluids. *J Chromatogr* 1976; 125: 503–510.

Two authors:

Vu-Duc T, Vernay A. Simultaneous detection and quantitation of O6-monoacetylmorphine, morphine and codeine in urine by gas chromatography with nitrogen specific and/or flame ionization detection. *Biomed Chromatogr* 1990; 4(2): 65–69.

Three or more authors:

Huestis MA et al. Monitoring opiate use in substance abuse treatment patients with sweat and urine drug testing. *J Anal Toxicol* 2000; 4(Suppl.3): 509–521.

Article in press:

Ladines CA et al. Impaired renal D1-like and D2-like dopamine receptor interaction in the spontaneously hypertensive rat. *Am J Physiol Regul Integr Comp Physiol* 2008 (in press).

Electronic publication ahead of print:

Teeuwen PHE. Doppler-guided intra-operative fluid management during major abdominal surgery: a systematic review and meta-analysis. *Int J Clin Pract* (accessed 21 November 2007, epub ahead of print).

Online serial:

Margolis PA et al. From concept to application: the impact of a community-wide intervention to improve the delivery of preventive services to children. Pediatrics [online] 2001; 108:e42. www.pediatrics.org/cgi/content/full/108/3/e42 (accessed 20 September 2001).

Corporate author:

The Cardiac Society of Australia and New Zealand . Clinical exercise stress testing. Safety and performance guidelines. *Med J Aust* 1996; 164: 282–284.

Anonymous author:

Anon. Coffee drinking and cancer of the pancreas. *BMJ* 1981; 283: 628.

Author with prefix and/or suffix in their name:

Humphreys Jnr, Sir Robert and Adams T. Reference style in the modern age. *J Bib Cit* 2008; 1: 1–10.

Article not in English:

Sokolov S et al. [Studies of neurotropic activity of new compounds isolated from *Rhodiola rosea* L.] Khim Farm Zh 1985; 19: 1367–1371 [in Russian].

Book references

Book by a single author or group of authors working together as a single author:

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ANEXO B - Carta de aceite Comitê de Ética

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

Grupo de Pesquisa e Pós-Graduação

Histórico do Projeto

Projeto

2017/0625 - IMPACTO DA ATUAÇÃO FARMACÊUTICA NO AJUSTE DE DOSE DE TERAPIA ANTIMICROBIANA COM CEFEPIME DE ACORDO COM A FUNÇÃO RENAL DO PACIENTE

Sigla:	
Pesquisador Responsável:	DANIEL MENDES DA SILVA
Data de Entrega:	24/11/2017
Origem:	HCPA >> Serviço de Farmácia
Realização:	HCPA >> Serviço de Emergência
Status Atual:	Aprovado