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Crowding in the emergency department (ED) occurs when the identified need for emergency services exceeds available resources for patient care in the ED, hospital, or both. The result of ED crowding is reduced quality of care, affecting morbidity, mortality and patient satisfaction. This is illustrated by two recent studies that demonstrate a direct association between ED crowding and an increased risk of mortality. In addition, delays in patient treatment also affect outcomes in conditions that benefit from short door-to-needle times, such as myocardial infarction, stroke, sepsis, meningitis and pneumonia. One of the most important indicators of quality of care and patient satisfaction is pain management, which is negatively affected by ED crowding as well. Therefore, understanding the causes, effects and solutions of ED congestion is important and subject of research questions.

To examine the complex logistic process of patient care on the ED, the process can be divided in three components: input, throughput and output. Input corresponds with aspects of patient inflow. Throughput corresponds with the process of patient care within the ED. Output corresponds with aspects of patient discharge from the ED.

Concerning input factors, ED visits are increasing. In our hospital, an inner city hospital in Amsterdam, a 17% increase to 49,000 ED visits per year was noted in the last eight years. A further rise is expected because of increasing numbers of self-referrals, ageing with shortage of care facilities, reduced number of hospital beds, waiting list problems, weakening of primary care services, illegal or uninsured patients and the demand for short diagnostic pathways. In addition, the Dutch government has intentions to concentrate acute care, which will put even more pressure on emergency departments. Research on input factors has focused on the patient with non-urgent complaints, such as an ankle sprain, normal cold, wound care, etc. Unlike the expectations, there is no evidence that this patient category is the cause of ED crowding and increased waiting times. In fact, it is the sick patient that needs hospital admittance and who is waiting for transfer to the ward that causes ED crowding and prolonged length of stay. This is mainly determined by the availability of hospital beds. So, improving output seems to be more important than reducing input to prevent ED congestion.

In this issue of the *Netherlands Journal of Medicine*, Vegting *et al.* describe throughput factors that influence the length of stay within the ED. They analysed completion times of all patients presenting to the ED during one month. The study results show that factors causing the throughput time to exceed a four-hour target were urgent triage category (ESI 3), age above 65, additional diagnostic investigations (CT scan) and evaluation by internal medicine, neurology or multiple specialities. Hospital admission as output factor was also associated with extended length of stay in the ED. Throughput factors have been evaluated at the ED of our hospital as well by a time analysis of internal medicine patients. In addition to the factors already mentioned, determinants we found were waiting time before arrival of the doctor, ED visit between 12.00 and 18.00 hours and the experience level of the resident. The door-to-doctor time and arrival times also contributed to the length of stay in the study of Vegting *et al.*; however these factors were not associated with the four-hour target.

Those patients who are evaluated by internal medicine are associated with a long throughput time in the ED. This has often to do with the complexity of the patients. Using our experience, the flow of these patients through the ED process can be improved by the following recommendations.

Firstly and foremost, acute care based on ‘Advanced Life Support’ (ALS) principles should be quick and effective.
These principles are aimed at identifying life-threatening problems. In addition, resuscitation and treatment is immediately started before a certain diagnosis is made. Since January 2011, it is mandatory that all physicians working in an ED in the Netherlands have followed special training in ALS.10

Secondly, ordering diagnostic tests immediately after triage accelerates the patient flow.11 This is especially useful when the doctor cannot directly see the patient for any reason. Almost every patient seen by internal medicine needs additional laboratory or radiographic examinations. Standardised symptom-based protocols have been developed that can be used for diagnostic work-up according to the presenting symptom, such as dyspnoea or abdominal pain. The availability of the results during the evaluation of the patient accelerates the diagnostic process in the ED.

Thirdly, monitoring of the diagnostic process is important, especially if multiple patients present simultaneously. To prevent crowding in the ED, only those diagnostic tests that contribute to making clinical decisions should be performed in the ED. This includes consultation of other specialties. To improve patient flow during peak hours two residents of internal medicine are scheduled in the ED of our hospital.

Fourthly, clinical decision-making supported by direct supervision reduces length of stay in the ED. In our hospital an internist is physically present at the ED and available for direct supervision during peak hours. The aim is to review every patient within two hours after presentation. The presence of an internist is also a valuable contribution in the training of residents by direct bedside teaching and supervision.

Fifthly, effective discharge planning is helpful to improve output. This can be achieved by having an overview of occupancy of hospital beds and effective communication about patient discharge from the ED. For logistic reasons, some hospitals create acute medical units to smooth the integrated hospital processes. Thinking one step ahead, after leaving the hospital, the patient may need extra care at home or in a nursing facility. Organising this care can substantially extend the admission period, blocking new admissions from the ED. To maintain the continuity of patient care, outflow of patients with support of community services must be arranged. This illustrates that continuity of acute care and crowding issues reach further than the ED.

In conclusion, patient flow at the ED is complex and crowding issues are here to stay. Numerous measures for improvement have been identified and can be implemented. Coordination of complex acute care is the expertise of the internist. Therefore, the internist fulfils a key position at the ED.

The expert in this field is the internist working in the ED department, whose specific domain is the complex undifferentiated patient with multiple disorders. The internist can adequately consider the (pathophysiological) context of a complex presentation and offers broad multidisciplinary knowledge and skills to achieve an integrated approach and treatment of these patients. Furthermore, the internist can identify these patients and initiate the coordination of acute care at the ED. In order to fulfil this role, the internist should be physically present in the ED. It is the strength of the internist to get the patient at the right place. This may also mean referral to another speciality by timely consultation.

In recent years, a new subspeciality of internal medicine has been developed: ‘Acute Medicine’. The internist with the subspeciality acute medicine is a generalist with specific expertise in acute care through extensive knowledge and skills in ALS, pain treatment and toxicology. In addition, this doctor has been trained in the coordination and logistics of acute care. Working at the interface between the first line, the emergency department, the clinic and the outpatient clinic, the internist is able to guide patient flow. Further professional development of this subspeciality will contribute to the quality and effectiveness of acute care and will have a positive effect on training, education and research in the field of acute medicine.

In conclusion, patient flow at the ED is complex and crowding issues are here to stay. Numerous measures for improvement have been identified and can be implemented. Coordination of complex acute care is the expertise of the internist. Therefore, the internist fulfils a key position at the ED.
REFERENCES

Chemokine and chemokine receptor blockade in arthritis, a prototype of immune-mediated inflammatory diseases

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ABSTRACT

Chemokines and chemokine receptors have been implicated in inflammatory cell recruitment and angiogenesis underlying the pathogenesis of rheumatoid arthritis (RA) and other inflammatory rheumatic diseases. Numerous CXC, CC, C and CX3C chemokines and their receptors have been detected in the arthritic synovium and numerous strategies, including biologics, peptide and other small molecule inhibitors of chemokines and their receptors have given promising results in preclinical studies performed in animal models of arthritis. However, most recent human RA trials using antibodies and synthetic compounds have failed. Reasons for negative results of these RA trials include overlapping actions of multiple chemokines, dose-dependency, both antagonistic and agonistic effects of chemokines, chemokine degradation by proteases, as well as effects of anti-inflammatory, regulatory cells. Recent studies have suggested that CCR1 may still be a good target and previous trials may have failed because of the need of sustained CCR1 occupancy throughout the treatment. Therefore, modulation of receptor occupancy may be a feasible option to increase the efficacy of chemokine receptor targeting.

KEYWORDS

Rheumatoid arthritis, chemokines, chemokine receptors, targeting

INTRODUCTION

In rheumatoid arthritis (RA) and other types of arthritis, leukocyte extravasation into the synovium occurs through the vascular endothelium. Numerous synovial chemotactic mediators termed chemokines and their receptors are involved in this process reviewed in references 1-6. Currently, there are more than 50 known chemokines and 19 chemokine receptors.4,6 Some of these chemokines and chemokine receptors are also involved in angiogenesis underlying synovitis.7-9 The release of chemokines antedates the onset of clinical arthritis.10,11

In this review, we will briefly summarise the most important chemokines and chemokine receptors in the pathogenesis of arthritis. Then we will give a critical update on recent anti-chemokine and anti-chemokine receptor approaches. As most of the initial studies have not been successful, we will try to give an explanation for this and make suggestions for future trials.

CHEMOKINES IN ARTHRITIS

Chemokines have been classified into the CXC, CC, C and CX3C supergene families (table 1). Their corresponding receptors have been termed CXCR, CCR, CR and CX3CR.4,6,11 Recently, the traditional name of chemokines was replaced by a unique designation of CXCL, CCL, XCL and CX3CL, considering all chemokines as ligands of their respective receptors.6,6,12 Apart from this structural classification, these mediators have been functionally classified as homeostatic and inflammatory chemokines.14
Nevertheless, these classifications are not fully justified as some primarily homeostatic chemokines involved in lymphoid development have also been implicated in inflammatory states, such as arthritis.1,4

**CXC chemokines in arthritis**

In CXC chemokines, two conserved C residues are separated by one unconserved amino acid. These mediators chemoattract neutrophils, lymphocytes and monocytes into the synovium. The underlying molecular mechanisms include leukocyte integrin expression and L-selectin shedding, cytoskeletal reorganisation, neutrophil degranulation and phagocytosis, as well as the production of proteases and other inflammatory mediators.1,4-6,9

The most relevant CXC chemokines involved in the pathogenesis of arthritis are CXCL1 (grot), CXCL4 (PF4), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (CTAP-III), CXCL8 (IL-8), CXCL9 (Mig), CXCL10 (IP-10), CXCL12 (SDF-1), CXCL13 (BCA-1) and CXCL16. All these chemokines are abundantly expressed in the sera, synovial fluids and tissues of arthritis patients.3-5,9-33

**CC chemokines**

CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14 (HCC-1), CCL15 (HCC-2), CCL16 (HCC-3), CCL17 (TARC), CCL18 (PARC), CCL19 (ELC), CCL20 (MIP-3α) and CCL21 (SLC) have all been detected in arthritic sera and synovia (table 1).25,30,50-68 Among these chemokines, CCL20 preferentially recruits Th17 cells,64 induces both osteoblast proliferation and osteoclast differentiation and collaborates with the RANK ligand system in the uncoupling between new bone formation and bone resorption in RA.59-73 CCL13 is also expressed by synovial fibroblasts, T cells and endothelial cells and follicular dendritic cells within the RA synovium.39-45 CXCL16 is secreted by synovial macrophages and fibroblasts and is involved in mononuclear cell recruitment into the RA synovium.39-45

**Table 1. Chemokines and chemokine receptors relevant for RA**

<table>
<thead>
<tr>
<th>Chemokine receptor</th>
<th>Chemokine ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR1 (A)</td>
<td>IL-8/CXCL8 (A,H), GCP-2/CXCL6</td>
</tr>
<tr>
<td>CXCR2 (A)</td>
<td>IL-8/CXCL8 (A,H), ENA-78/CXCL13 (A), grot/CXCL4 (A), CTAP-III/CXCL7, GCP-2/CXCL6</td>
</tr>
<tr>
<td>CXCR3 (A)</td>
<td>IP-10/CXCL10, PF4/CXCL4, Mig/CXCL9</td>
</tr>
<tr>
<td>CXCR4 (A)</td>
<td>SDF-1/CXCL12</td>
</tr>
<tr>
<td>CXCR5</td>
<td>BCA-1/CXCL13</td>
</tr>
<tr>
<td>CXCR6</td>
<td>CXCL16 (A)</td>
</tr>
<tr>
<td>CXCR7</td>
<td>ITAC/CXCL11, SDF-1/CXCL12</td>
</tr>
<tr>
<td>CXCR1 (A,H)</td>
<td>MIP-1α/CCL3 (A), RANTES/CCL5 (A), MCP-3/CCL7, HCC-1/CCL14, HCC-2/CCL15, HCC-4/CCL16</td>
</tr>
<tr>
<td>CCR2 (A)</td>
<td>MCP-1/CCL2 (A,H), MCP-3/CCL7, HCC-1/CCL14</td>
</tr>
<tr>
<td>CCR3</td>
<td>RANTES/CCL5, MCP-2/CCL8, MCP-3/CCL17, HCC-2/CCL15</td>
</tr>
<tr>
<td>CCR4</td>
<td>TAR/CCL17, CKL6</td>
</tr>
<tr>
<td>CCR5 (A,H)</td>
<td>MIP-1α/CCL3 (A), RANTES/CCL5 (A), MCP-2/CCL8, HCC-1/CCL14</td>
</tr>
<tr>
<td>CCR6</td>
<td>MIP-3α/CCL20</td>
</tr>
<tr>
<td>CCR7</td>
<td>SLC/CCL21</td>
</tr>
</tbody>
</table>

*Already targeted in animal models (A) or human (H) trials. See text for abbreviations*
C and CXC chemokines in RA
The C chemokine family contains two members, XCL1 (lymphotactin) and XCL2 (SCM-1f). Among them, XCL1 is involved in T cell accumulation in the RA joint. The single member of the CX3C family is CX3CL1 (fractalkine). This chemokine is chemotactic for mononuclear cells, mediates T cell adhesion and cytokine production, and regulates the cytoskeletal structure, proliferation and migration of synovial fibroblasts. CXCL1 is also an angiogenic mediator and has been associated with rheumatoid vasculitis and accelerated atherosclerosis leading to increased cardiovascular morbidity in RA.

CHEMOKINE RECEPTORS IN ARTHRITIS
Chemokine receptors are 7-transmembrane domain receptors expressed on the target cells. Some chemokine receptors, such as CXCR2, CCR1, CCR2, CCR3 or CCR5, have multiple ligands, while others including CXCR4, CCR5, CXCR6, CCR8 or CCR9 are specific receptors for one single ligand. In general, all CXCRs have been implicated in the pathogenesis of arthritis. CXCR1 and CXCR2 recognise the most relevant inflammatory and angiogenic CXC chemokines described above. CXCR3 may be the most important receptor in leukocyte homing into Th1 type inflammatory sites, such as the RA synovium. As described above, CXCR4 is involved in CXCL12-dependent ingress of lymphocytes into the RA synovium. CXCR4, CXCR5 and CXCR6 bind their respective homeostatic chemokine ligands, CXCL12, CXCL13 and CXCL16. Thus, as mentioned above, these CXCRs are involved in both physiological lymphoid organisation and synovial lymphoid neogenesis.

Among CCRs, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6 and CCR7 are abundantly expressed in the RA synovium and on synovial cells. CCR2 and CCR3 are also present on articular chondrocytes. CCR5 may be the most prominent CCR characterising Th1 inflammatory infiltrates. In some studies, a single nucleotide polymorphism leading to the production of the truncated f32-CCR5 non-functional receptor allele was found to be protective against RA including extra-articular symptoms and joint erosions, but results have been variable. The protective role of this polymorphism was also suggested in juvenile psoriatic arthritis. CCR6 is involved in the ingress of Th17 lymphocytes into the rheumatoid joint. CCR6 has been associated with synovial lymphoid neogenesis in murine arthritis. In a comparative study on CCRs, peripheral blood monocytes mainly expressed CCR1 and CCR2, suggesting that these receptors were involved in monocyte recruitment from the circulation. In contrast, CCR3 and CCR5 expression was upregulated in RA synovial fluids indicating that these CCRs were important in monocyte retention in the joint. Regarding the C and CX3C chemokine receptors, XCR1 is expressed on RA synovial lymphocytes, macrophages and fibroblasts, while CX3CR1 has been detected on macrophages and dendritic cells. CCR7 has been implicated in the recruitment of Th1 type lymphocytes into the joint.

TARGETING OF CHEMOKINES AND CHEMOKINE RECEPTORS
Chemokines and chemokine receptors may be targeted by indirect, non-specific as well as by direct, chemokine-specific approaches. These strategies have been tested in animal models of arthritis, in vitro cultures of human RA synovial cells and tissues, as well as in a limited number of human RA clinical trials. Inhibition of chemokine and chemokine receptor expression by immunosuppressive therapy
Some non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, traditional disease-modifying antirheumatic drugs (DMARD) and biologics exert multiple anti-inflammatory actions including chemokine and chemokine receptor inhibition. In early studies, NSAIDs and corticosteroids attenuated CXCL8 and CCL2 production in vitro and as well as in arthritis models. A recently developed dual cyclooxygenase-lipoxygenase inhibitor, ML3000, downregulated CXCL9, CXCL10 and CXCL11 expression in RA synovial fibroblasts. Among traditional DMARDs, sulfasalazine, sulfapyridine, methotrexate (MTX) and leflunomide inhibited the production of various CXC and CC chemokines in synovial cell and explant cultures in vitro, as well as in animal models of arthritis and RA in vivo. There have been an increasing number of studies with biologics, primarily anti-TNF agents. Infliximab and etanercept may suppress the release of CXCL1, CXCL8, CXCL10, CXCL16, CCL2, CCL5, CCL20, CX3CL1 and possibly other chemokines in RA. The IL-6 receptor inhibitor tocilizumab also suppressed CCL20 production in RA. As IL-6 signalling plays a crucial role in the stimulation of chemokine production in RA, tocilizumab may inhibit the release of other chemokines as well. B cell inhibition by rituximab alters the CXCL8 network and decreases CCL5 production. Efficacy of rituximab has been associated with surface CCR5 density. With respect to chemokine receptors, TNF-α blockade also reduced CCR3, CCR5, CCR6 and CX3CR1 expression on T cells and resulted in the clearance of CXCR3· T
cells from the synovium. The efficacy of rituximab was correlated with increased CCR5 density on peripheral blood T cells in RA. Chemokine inhibition by biologics may have relevance for safety of anti-TNF therapy as infliximab reduced the secretion of CCL2, CCL3 and CCL5 in response to Mycobacteria. Some other synthetic compounds, as well as natural products, may also influence chemokine secretion. For example, antioxidants, such as N-acetyl-L-cysteine and 2-oxothiazolidine-4-carboxylate, the bioflavonoid quercetin, as well as the lipid-lowering simvastatin, inhibited the expression of CCL8 and CCL2 by activated, cultured human synovial fibroblasts.

Specific chemokine targeting

In various animal models of arthritis, neutralising antibodies to CXCL1, CXCL5, CCL2, CCL3, CCL5, CCL7, CCL8, CCL14, CCL15 and CCL16 also improved rat arthritis. Some traditional Oriental medicines, such as triptolide, lingzhi, curcumin, tongbiling, honokiol, cool-cold and others exert antiarthritic effects, which may, in part, be explained by chemokine and chemokine receptor inhibition.

In summary, after promising preclinical studies in arthritis models using antibodies and peptide inhibitors to chemokines, only one human RA trial yielding negative results has been published. This trial was completed in 2006 and not followed by others, suggesting that targeting of a single chemokine may not be effective in arthritis. Preclinical studies using combined chemokine blockade already suggested that simultaneous targeting of multiple chemokines may be the future strategy. As chemokine receptors may recognise multiple inflammatory chemokine ligands, more trials have been conducted using CCR antagonists.

Chemokine receptor blockade: how to proceed after disappointing clinical trials?

Some CXCR antagonists have been used in animal models, but they were not tested in human RA. For example, an anti-CXCR3 antibody inhibited AIA. Synthetic oral antagonists of CXCR1, CXCR2 and CXCR4 inhibited arthritis in various rodent models. To our knowledge, no clinical trial results obtained with any CXCR antagonists in arthritis have been published. CCR1, CCR2 and CCR5 bind multiple CC chemokine ligands including CCL3, CCL5, CCL7, CCL8, CCL14, CCL15 and CCL16 that have been implicated in the pathogenesis of RA. Therefore, numerous synthetic or biological CCR1, CCR2 and CCR5 antagonists have been developed in recent years. Dual targeting of CCR2 and CCR5 is underway.

CCR1 is a receptor for CCL3, CCL5, CCL7, CCL14, CCL15 and CCL16 (table 1). Among CCR1 antagonists, in early preclinical studies, J-113863 diminished synovitis and joint destruction in murine collagen-induced arthritis (CIA). Met-RANTES, a dual CCR1/CCR5 antagonist, inhibited both murine CIA and rat AIA. This was followed by the development and introduction of two oral CCR1 antagonists, CP-481,715 and MLN3897, to human RA trials. CP-481,715 was evaluated in a phase I clinical trial to assess pharmacokinetics and safety. It was administered to 78 healthy individuals in escalating doses up to 3000 mg. This drug was well-tolerated.

CP-481,715 has also been evaluated in a two-week phase Ib, proof-of-concept study in RA patients using a dose of 300 mg per eight hours. Altogether 16 RA patients were randomised 3:1 with active:placebo treatment for 14 days, and it decreased the number of total and intimal macrophages, as well as CCR1+ cells in the synovium. About one-third of the patients also fulfilled the ACR20 criteria for clinical improvement. In a subsequent phase IIa study, RA patients with active disease despite MTX treatment received either 10 mg of MLN3897 or placebo orally once daily with concomitant MTX therapy. Although MLN3897 was well-tolerated, no difference in ACR20 was found between the active and placebo group. Interestingly,
MLN3897 was associated with a relatively high degree (≥ 90%) of CCR1 occupancy throughout the trial as determined by CCL3 internalisation assay.169 CCR2 recognises CCL2, CCL7 and CCL16 (Table 1). Some CCR2 inhibitors have also entered animal studies and then clinical trials.86 While low doses of the MC-21 anti-CCR2 monoclonal antibody markedly improved murine CIA, high doses of this antibody rather had pro-inflammatory effects.88 MK0812, another small molecule CCR2 inhibitor, had no effect on the severity of CIA.167 In a phase IIa clinical trial with a CCR2 blocking antibody MLN1202, 32 patients with active RA received three infusions of either placebo or anti-CCR2 antibody at 0.5 mg/kg or 1.5 mg/kg over a period of six weeks. The antibody reduced the levels of free CCR2 on CD14+ monocytes; however, no clinical benefit could be demonstrated.168 CCR5 binds CCL3, CCL5, CCL8 and CCL14 (Table 1). As discussed above, in earlier studies, Met-RANTES and other small molecule antagonists, such as SCH-X of CCR5, showed some efficacy in preclinical arthritis studies.35,79,85 Recently, a small molecule CCR5 antagonist, AZD3562, was tried in preclinical, phase I and IIb studies. Ligand-binding and chemotaxis studies supported the biological activity of this compound. In the phase IIb trial, 371 patients with active RA received 20 mg, 50 mg, 100 mg or 150 mg oral AZD3562 once daily, placebo or open-label etanercept 50 mg subcutaneously once weekly. There was no significant difference in the number of patients receiving the active compound or placebo. Furthermore, etanercept was more effective than AZD3562 or placebo.74 A phase Ib trial was conducted with SCH351125, a small molecule oral CCR5 inhibitor. Among 32 patients with active RA, 20 received the active compound and 12 received placebo. No synovial, MRI or clinical efficacy could be proven.75 Another CCR5 inhibitor, maraviroc, has been tried in phase II–III trials in HIV infection and AIDS, as well as to a phase II trial in RA.184

Thus, CCR2 and CCR5 blockade yielded disappointing results in RA, and results for CCR1 blockade have been variable. Do we now have to bury the idea of blocking chemokines and their receptors in arthritis and other immune-mediated inflammatory disorders? Maybe we should think again. There have been several issues that may interfere with the efficacy of chemokine and chemokine receptor blockade in RA (Table 2).4,5,52,69,85 As discussed above and also shown in Table 2, the chemokine system is redundant. Therefore, targeting a single chemokine or a receptor specific for one ligand may not be sufficient.158,159 Multiple chemokines and chemokine receptors have been simultaneously targeted in animal models; however, human trials have not yet been conducted.158,159,177,180 Moreover, noncompetitive antagonism and inverse agonism may occur simultaneously on the chemokine receptor level.168 The ultimate effects may be dependent on the dose of the CCR antagonists.169 Chemokine cleavage by proteases may alter their function,187,189,190 and thus, in the presence of matrix metalloproteinases, such as in the inflamed joint, the function of chemokines may be altered, and therefore the effects of chemokine inhibition may be different than expected. The paradoxical effect may also be explained by the fact that specific chemokine receptors are expressed by both inflammatory and anti-inflammatory, regulatory T cells (Tregs). Thus, chemokine/receptor blockade may interfere with the migration of cells, such as Tregs with anti-inflammatory properties.191,192 Finally, as discussed above, some chemokines, such as CXCL12, CXCL13, CXCL16, CCL17, CCL18, CCL19 and CCL21, are involved in both homeostatic and inflammatory processes.1,14,49,44,44,47 Chemokine blockade may interfere with homeostatic functions.167

In order to determine the future of chemokine receptor blockade, a recent study assessed the effects of specific chemokine receptor blockade on monocyte migration towards synovial fluid in vitro. Monocytes were chosen, since synovial macrophages derived from monocytes are key producers of pro-inflammatory cytokines and chemokines and they represent biomarkers sensitive to change after effective treatment.33,46 Therefore, an in vitro monocyte migration assay was used to determine the effects of CCR1, CCR2 and CCR5 inhibition. Monocyte chemotaxis was induced by CCL2, CCL5 or by an RA synovial fluid pool and the effects of anti-CCR1, anti-CCR2 and anti-CCR5 blocking antibodies, as well as those of BX147, a small molecule CCR1 inhibitor, were tested. As expected, anti-CCR2 and anti-CCR5 antibodies inhibited CCL2- and CCL5-induced chemotaxis, respectively. However, the anti-CCR2 and anti-CCR5 antibodies did not influence RA synovial fluid-mediated monocyte migration, not even when used in combination. In contrast, both the anti-CCR1 antibody and the CCR1 synthetic inhibitor blocked RA synovial fluid-induced monocyte chemotaxis. These results suggest that while CCR2 and CCR5 may not be critical for monocyte migration into synovial compartments, CCR1 seems to mediate this process.186 Indeed, CCR2 and CCR5 antibody blockade

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**Table 2. Examples of potential difficulties and caveats in human chemokine and chemokine receptor blockade trials**

- Redundancy of the chemokine system
- Agonist action of certain ligands on one receptor, and antagonist action on others
- Cleavage of chemokines by proteases
- Unwanted inhibition of anti-inflammatory cells
- Interference with homeostatic function
- Levels of receptor occupancy were not high enough at all times

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Szekanecz et al. Chemokines and chemokine receptors in arthritis.
failed to reduce synovial cell infiltration in clinical trials.\textsuperscript{68,73} Although preclinical studies indicated that dual targeting of CCR2 and CCR5 may be beneficial in animal models of arthritis,\textsuperscript{77} these data raise concerns about potential efficacy of CCR2/CCR5 blockade in RA patients.\textsuperscript{82} In contrast, CCR1 blockade inhibited synovial macrophage infiltration in a proof-of-principle study in RA patients\textsuperscript{72,73,80} and also in the recent study showing the effects of \textit{in vitro} migration towards synovial fluid.\textsuperscript{81} Therefore, the fact that CCR1 blockade failed in some clinical trials does not necessarily mean that CCR1 is not a good target.\textsuperscript{82} It appears critical to achieve very high levels of receptor occupancy at all times during the day in order to inhibit monocyte migration into the synovial compartment \textit{in vivo}.\textsuperscript{169} Indeed, sustained CCR1 occupancy has been associated with effective anti-inflammatory response in other models of inflammation.\textsuperscript{193}

\textbf{SUMMARY}

In this review, we have discussed the potential role of chemokines and chemokine receptors in the pathogenesis of arthritis. Numerous CXC, as well as some CC and CXC chemokines and their respective receptors, have been implicated in leukocyte ingress into the inflamed synovium. Despite promising results in preclinical studies using anti-chemokine and anti-chemokine receptor biologics and small molecule compounds, nearly all human RA trials failed. Recent studies suggest that, at least with CCR1 inhibitors, chemokine receptor occupancy during the whole day is critical. This insight may open new opportunities for future clinical trials in RA as well as other inflammatory conditions.

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Hepatic and renal manifestations in autosomal dominant polycystic kidney disease: a dichotomy of two ends of a spectrum

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder. It is the most common genetic cause of end-stage renal disease. One frequent extra-renal manifestation is hepatic cyst formation. The majority of ADPKD patients develop complications as a result of renal cyst formation; however, a small proportion develop extensive hepatic disease with minor renal features. Both phenotypes seem to represent the spectrum of ADPKD. This review discusses the current understanding of the pathogenesis of the disease, its manifestations and the mechanisms of cyst formation. Furthermore, it focuses on monitoring the disease and the treatment options currently available.

KEYWORDS

ADPKD, hepatic phenotype, polycystic liver, diagnosis, treatment

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of end-stage renal disease. It is a multisystem disorder and the primary phenotype is characterised by renal cyst growth causing enlargement of the kidneys. The most common extra-renal manifestation is hepatic cyst formation. While the majority of ADPKD patients develop complications secondary to renal polycystic disease, there appears to be a proportion of patients who have limited renal disease but extensive hepatic disease. Both subsets appear to represent the spectrum of ADPKD and require a different approach to diagnosis and management. Most of the topical reviews have focused on the renal aspects of the disease, and less so on the hepatic phenotype. In order to address this issue we provide a detailed overview of the current literature with a focus on both the renal and hepatic phenotype of ADPKD.

RENA L M A N I F E S T A T I O N S  O F  A D P K D

The clinical course of ADPKD is highly variable, partly due to contribution of gene-modifier effects (see textbox). Renal cysts vary in size and appearance and may arise from all segments of the nephron. The formation of cysts leads to the destruction of renal parenchyma and causes renal enlargement, thereby disrupting the normal architecture of the kidney. The initial phase of the disease is often clinically silent. Symptoms arise late in adulthood and are related to the progressive growth of the kidneys, as the size of the kidneys increases from a normal size of 150 to 200 cm³ to >1500 cm³ per kidney. Flank pain, haematuria, renal colic, recurrent urinary tract infection and arterial hypertension may be presenting symptoms. Hypertension is the most common manifestation in ADPKD and is present in about 50% of patients aged 20 to 34 years with normal renal function. Despite the progressive growth of cysts in both kidneys, renal function is well preserved as long as functioning nephrons undergo compensatory hypertrophy. Gener ally, renal function is maintained until the 4th to 6th decade of life. However, once the compensatory mechanism of the kidneys fails, a rapid decline in renal function occurs. The progressive disease ultimately leads to end-stage renal disease, and chronic renal failure presents in about 50% of patients by the age of 60.
**Monitoring Progression of Renal Disease**

The initial step in diagnosing ADPKD is renal ultrasound. The presence of at least three unilateral or bilateral renal cysts in patients aged 15 to 39 years and of two cysts in each kidney in patients aged 40 to 59 years is sufficient for diagnosis in at-risk individuals from ADPKD families. Four cysts or more in each kidney are required in at-risk individuals aged >60 years. In families with known PKD1 gene mutation, diagnostic criteria are expressed in number and location of renal cysts related to age. Monitoring of disease progression in ADPKD differs from other renal diseases. In ADPKD, renal function decreases only late in the course of the disease due to compensatory mechanisms of intact nephrons. In order to prevent this decline in renal function, therapies should be targeted to patients in an early phase of their disease. The Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) demonstrated that total kidney and cyst volume increase exponentially (±5% annually), even prior to the loss of kidney function. Moreover, the rapidity of increase of renal volume is associated with a future decline in renal function. Finally, ultrasound is less accurate for determining small changes in renal volume and measuring large kidneys when compared with magnetic resonance imaging (MRI). Although the relationship between kidney volume and renal function may be true for the population at large, individual patients with a high total renal volume may have preserved kidney function.

**Management of Renal ADPKD**

To date there is no treatment available to delay disease progression in patients with ADPKD. Current management recommendations for patients with ADPKD include optimal blood pressure control and sufficient fluid intake. Furthermore, smoking, long-term administration of nephrotoxic agents and probably excessive caffeine intake should be avoided, as caffeine may promote renal cyst growth. However, it remains uncertain whether adequate hypertension management delays renal failure in ADPKD.

In patients with chronic pain refractory to conservative measures, surgical interventions including surgical cyst fenestration or cyst aspiration in combination with injection of sclerosing agents can be considered. Renal transplantation is the treatment of choice for end-stage renal disease in patients with ADPKD. The procedure for renal transplantation for ADPKD differs from most other indications as the native polycystic kidney(s) may necessitate removal due to space constraints secondary to massive renal enlargement. Several medical options aimed to slow cyst growth and thereby delay the onset of end-stage renal disease are currently being explored.

Somatostatin analogues are thought to stabilise cyst volumes in ADPKD patients. Indeed, several randomised controlled trials demonstrated a beneficial effect of somatostatin analogues on polycystic kidney volumes in patients with ADPKD. However, due to the short duration of trials, the effect on renal function and end-stage renal disease could not be determined. Mammalian target of rapamycin (mTOR) inhibitors are another class of drugs that have been suggested to delay the progression of ADPKD. However, two recent trials using everolimus and sirolimus, both mTOR inhibitors, failed to influence the decline in renal function or to halt polycystic kidney growth. Finally, Tolvaptan is a vasopressin V2 receptor antagonist that inhibits renal cyst growth in an animal model for polycystic kidney disease. A prospective, three-year, placebo-controlled trial of Tolvaptan (TEMPO 3-4) is now ongoing to determine whether this drug is safe and effective in delaying the progression of ADPKD.

**A Dichotomy**

The renal phenotype dominates in the largest proportion of ADPKD patients. However, in a subset of patients, hepatic cysts overtake renal cysts and patients suffer more from their polycystic liver. The overall prevalence of hepatic cysts in patients with ADPKD is 83%. The prevalence increases with increasing age and decreasing renal function and is the highest in patients with end-stage renal disease. However, most patients have only a few hepatic cysts and polycystic livers, arbitrarily defined as >20 cysts, occur infrequently. Indeed, there are a number of risk factors for polycystic livers in ADPKD. Sex appears to be the most defining risk factor; females are more likely to suffer from a polycystic liver. Furthermore, female patients with prior pregnancies and/or use of oestrogens have more and larger liver cysts. In addition, renal cyst volume is correlated with a more severe hepatic disease. Nonetheless, a proportion of ADPKD patients present both renal cysts and normal renal function but extensive hepatic disease. These patients are not threatened by renal complications of the disease, but clearly develop symptoms secondary to hepatic polycystic disease. Testament to this observation are the cohorts of ADPKD patients recruited for clinical trials that aimed at reduction of liver volume. For example, ADPKD patients with polycystic livers participated in a trial examining lanreotide treatment. These patients showed both an increased average renal volume of 1000
ml (normal 154-202 ml per kidney) and an extensive mean liver volume of 5119 ml (normal 1500 ml) though without renal complications; few of these patients had hypertension, and renal function was normal in most cases. These findings emphasise the importance of a different approach to ADPKD patients with polycystic livers than to ADPKD patients with renal manifestations. This dichotomy of both extensive polycystic kidney disease and few hepatic cysts and extensive hepatic cysts and relatively few renal cysts is illustrated in figure 1 by panel A, B and C respectively.

**HEPATIC MANIFESTATIONS OF ADPKD**

Liver cysts arise from cholangiocytes as the result of ductal plate malformation. Several pathways are involved in the growth of hepatic cysts (seeTextbox). Symptoms are related mainly to liver size, as polycystic livers can grow to up to ten times their normal size. Compression of adjacent abdominal and thoracic organs may lead to abdominal pain, abdominal distention, early satiety, nausea and vomiting. Clinical course and indications for interventions are therefore highly dependent of total liver volume.

**MONITORING PROGRESSION OF HEPATIC CYSTS**

Liver function is generally maintained during the whole course of the disease. Few patients demonstrate abnormalities in liver function or liver enzymes. There are no specific laboratory tests that predict the presence of liver cysts in ADPKD. Hepatic cysts are detected using ultrasound. The CRISP study showed a higher prevalence of hepatic cysts in early ADPKD using MRI compared with ultrasound. The implication of early detection remains unclear, as interventions are currently considered as soon as symptoms develop. Because oestrogens stimulate cholangiocyte proliferation and enhance cyst formation, it is advised to avoid the use of oestrogens. Imaging of hepatic cysts should be guided by symptom management.

**TREATMENT OPTIONS FOR HEPATIC CYSTS IN ADPKD**

The main indications for treatment of hepatic cysts are abdominal pain, abdominal mass, fullness and early satiety. A variety of surgical and medical options exist for the treatment of hepatic cysts in ADPKD. Among the surgical options are aspiration in combination with sclerotherapy, fenestration, segmental hepatic resection and liver transplantation. Aspiration and subsequent sclerosis of hepatic cysts is best performed in a dominant and large, likely symptomatic, cyst. In laparoscopic fenestration multiple cysts are unroofed in one session. Segmental hepatic resection may be considered in cyst rich segments in the presence of at least one predominantly normal segment. All surgical options are invasive, and carry a certain morbidity and mortality risk but provide relatively instant relief. However, recurrence of treated cysts is not infrequent (21 to 39%). Liver transplantation is the only curative option and is indicated for severe polycystic livers with extreme disabling symptoms or untreatable complications. Combined liver-kidney transplantation should be considered in patients who are listed for liver transplantation and have an impaired kidney function (GFR <30 ml/min). Liver transplantation is the only curative option and is indicated for severe polycystic livers with extreme disabling symptoms or untreatable complications. Combined liver-kidney transplantation should be considered in patients who are listed for liver transplantation and have an impaired kidney function (GFR <30 ml/min). Current medical options in the treatment of ADPKD are somatostatin analogues and mTOR inhibitors.

**Figure 1.** A dichotomy in ADPKD phenotypes. Panel A shows a coronal computed tomography of a patient with ADPKD presenting extensive renal disease and relatively few hepatic cysts. By contrast, panel B and C show a patient with ADPKD presenting extensive hepatic disease and relatively few renal cysts.
Somatostatin analogues, such as lanreotide and octreotide, are cyclic adenosine monophosphate (cAMP) level inhibitors and decrease fluid secretion and cell proliferation in many cell types, such as cholangiocytes.14,38-40 The effect of these agents, especially long-acting somatostatin analogues, has been studied in a number of trials in polycystic livers. On the short term (up to 6 and 12 months), these studies show regression of liver volume (-5% to -2.9%), contrasting the increase in the placebo groups (+0.9% to +1.6%).14,38-40

mTOR inhibitors are another class of drugs known to inhibit liver cyst growth. In a study performed to optimise the immunosuppressive strategy after renal transplantation, a retrospective measurement of liver volume was performed to elucidate whether sirolimus had any effect on the liver volume.41 Sirolimus reduced liver volume by 11.9%, whereas tacrolimus caused an increase in liver volume of 14.2%. mTOR inhibitors are another class of drugs known to inhibit liver cyst growth. In a study performed to optimise the immunosuppressive strategy after renal transplantation, a retrospective measurement of liver volume was performed to elucidate whether sirolimus had any effect on the liver volume.41 Sirolimus reduced liver volume by 11.9%, whereas tacrolimus caused an increase in liver volume of 14.2%.

In conclusion, somatostatin analogues and probably mTOR inhibitors are the first two identified drug classes that change the natural course of the polycystic disease, although the effect is still limited. Effects of prolonged therapy of somatostatin analogues or mTOR inhibitors on liver volume are still unknown.

**Conclusion**

The majority of ADPKD patients develop complications due to renal polycystic disease; however, a proportion of patients present with extensive hepatic disease and possess only minimal renal features. Both phenotypes of this disease appear to represent either end of a spectrum and need specific approaches in monitoring and treatment of disease. After diagnosis, primarily established by imaging modalities, renal management should be focused on monitoring blood pressure and treating hypertension. Nephrological follow-up should be focused on renal function and renal volume. Renal transplantation may be considered in end-stage renal disease. In contrast, monitoring the hepatic phenotype should focus on therapeutic interventions in case of gastrointestinal symptoms regardless of cyst extent, as liver function stays intact.

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The dietary intake of saturated fatty acids (SAFA) is associated with a modest increase in serum total cholesterol, but not with cardiovascular disease (CVD). Replacing dietary SAFA with carbohydrates (CHO), notably those with a high glycaemic index, is associated with an increase in CVD risk in observational cohorts, while replacing SAFA with polyunsaturated fatty acids (PUFA) is associated with reduced CVD risk. However, replacing a combination of SAFA and trans-fatty acids with n-6 PUFA (notably linoleic acid) in controlled trials showed no indication of benefit and a signal toward increased coronary heart disease risk, suggesting that n-3 PUFA may be responsible for the protective association between total PUFA and CVD. High CHO intakes stimulate hepatic SAFA synthesis and conservation of dietary SAFA. Hepatic de novo lipogenesis from CHO is also stimulated during eucaloric dietary substitution of SAFA by CHO with high glycaemic index in normo-insulinaemic subjects and during hypocaloric high-CHO/low-fat diets in subjects with the metabolic syndrome. The accumulation of SAFA stimulates chronic systemic low-grade inflammation through its mimicking of bacterial lipopolysaccharides and/or the induction of other pro-inflammatory stimuli. The resulting systemic low-grade inflammation promotes insulin resistance, reallocation of energy-rich substrates and atherogenic dyslipidaemia that conversely give rise to increased CVD risk. We conclude that avoidance of SAFA accumulation by reducing the intake of CHO with high glycaemic index is more effective in the prevention of CVD than reducing SAFA intake per se.

**KEYWORDS**

Saturated fatty acids, carbohydrates, diet heart, cardiovascular disease, fat
A high serum total cholesterol, and especially LDL cholesterol, is associated with an increased risk of CVD, whereas a high HDL cholesterol has a protective association. The serum total cholesterol/HDL cholesterol ratio is the consensus risk factor for the estimation of coronary heart disease risk. The reduction of this ratio by 1 point is classically associated with a coronary heart disease risk reduction of 52%. The metabolic syndrome, also called the insulin resistance syndrome, which is characterised by obesity, impaired glucose homeostasis, hypertension and atherogenic dyslipidaemia ('deadly quartet'), is a major risk factor for CVD. Similarly, atherogenic dyslipidaemia, which is characterised by elevated triglycerides, small dense LDL particles and reduced HDL cholesterol ('deadly lipid triad'), is also a major risk factor for CVD. These small dense LDL particles are susceptible to structural modifications by oxidation and notably oxidised LDL particles affect atherosclerotic plaque formation by promoting foam cell generation, endothelial dysfunction and local inflammation.

An increase in the consumption of SAFA by 1 energy percent (en%) raises serum total cholesterol by 0.052 mmol/l. However, in the same study, the total cholesterol of subjects consuming 15 en% SAFA ranged from 4 to 6 mmol/l, indicating that most variation in the serum total cholesterol is not on account of the differences in SAFA intake per se. Because of the presumed relationship between SAFA and CVD, it is nowadays recommended to replace dietary fat, and especially SAFA, by cis-unsaturated fatty acids. Between 1987/1988 and 1997/1998 the intake of cis-unsaturated fatty acids, refined CHO and monosaccharides and disaccharides in the Netherlands increased at the expense of fat, SAFA and trans-fatty acids. In this review, we will evaluate the current consensus on the relationship between SAFA and CVD while the consequences of replacing SAFA by CHO, and notably oxidised LDL particles affect atherosclerotic plaque formation by promoting foam cell generation, endothelial dysfunction and local inflammation.

**Lipoproteins, Cholesterol, SAFA and CVD**

A high serum total cholesterol, and especially LDL cholesterol, is associated with an increased risk of CVD, whereas a high HDL cholesterol has a protective association. The serum total cholesterol/HDL cholesterol ratio is the consensus risk factor for the estimation of coronary heart disease risk. The reduction of this ratio by 1 point is classically associated with a coronary heart disease risk reduction of 52%. The metabolic syndrome, also called the insulin resistance syndrome, which is characterised by obesity, impaired glucose homeostasis, hypertension and atherogenic dyslipidaemia ('deadly quartet'), is a major risk factor for CVD. Similarly, atherogenic dyslipidaemia, which is characterised by elevated triglycerides, small dense LDL particles and reduced HDL cholesterol ('deadly lipid triad'), is also a major risk factor for CVD. These small dense LDL particles are susceptible to structural modifications by oxidation and notably oxidised LDL particles affect atherosclerotic plaque formation by promoting foam cell generation, endothelial dysfunction and local inflammation.
monounsaturates and PUFA will be examined with regard to their influence on atherogenic dyslipidaemia.

SAFA AND CVD

A recent meta-analysis of prospective cohort studies showed that the intake of SAFA is not associated with an increased risk of coronary heart disease, stroke or those two combined (i.e. cardiovascular disease, CVD), before or after adjustment for serum total cholesterol. Additionally, the consumption of milk and milk products was not related to CVD in a meta-analysis of prospective cohort studies. Consumption of milk and milk products may even decrease CVD risk, although this meta-analysis of prospective cohort studies was not supported by a recent prospective cohort study in the Netherlands.

REPLACING SAFA BY CHO

Replacing 5 en% SAFA with 5 en% CHO reduced serum total cholesterol by 0.18 mmol/l, LDL cholesterol by 0.16 mmol/l and HDL cholesterol by 0.05 mmol/l, increased the serum triglycerides by 0.11 mmol/l and had no effect on the total cholesterol/HDL cholesterol ratio. LDL cholesterol reduction from isocaloric substitution of SAFA by CHO is accompanied by an increase in the amount of atherogenic small dense LDL particles and a decrease in the less atherogenic large LDL particles. Because of the increase in triglycerides and small dense LDL and no change in the total cholesterol/HDL cholesterol ratio, replacing SAFA by CHO seems unfavourable with regard to CVD prevention.

A pooled analysis of 11 cohort studies showed that replacing 5 en% SAFA by CHO was associated with a slightly increased risk of coronary events (7%), but there was no difference in mortality. In practice, however, SAFA are often replaced by CHO with a high glycaemic index. A subsequent analysis by Jakobsen et al. showed that replacement of 5 en% SAFA by CHO with a low glycaemic index was associated with a non-significant reduction in CVD risk, while replacing SAFA by CHO with a high glycaemic index was associated with a 33% increased risk of myocardial infarction.

REPLACING SAFA BY MONOUNSATURATED FATTY ACIDS

Replacing 5 en% SAFA by 5% monounsaturated fatty acids reduced total cholesterol by 0.21 mmol/l, LDL cholesterol by 0.20 mmol/l, and HDL cholesterol by 0.01 mmol/l, and increased the serum triglycerides by 0.01 mmol/l. The 0.145 reduction in the total cholesterol/HDL cholesterol ratio is predicted to translate into a coronary heart disease risk reduction of 7.5%. However, in the recent pooled analysis of prospective observational cohorts by Jakobsen et al., the intake of monounsaturated fatty acids was associated with a 15% higher risk of CVD events, but not with coronary heart disease mortality. This outcome contrasts with the beneficial effects of the so-called Mediterranean diet, which is typically high in monounsaturated fatty acids, and the theoretical decrease of the total cholesterol/HDL cholesterol ratio, when SAFA are replaced by monounsaturated fatty acids. Consequently, it was recently concluded that there is insufficient evidence to advise the replacement of SAFA by monounsaturated fatty acids.

REPLACING SAFA BY N-6 AND N-3 PUFA

Replacing 5 en% SAFA by 5 en% PUFA decreased total cholesterol by 0.29 mmol/l, LDL cholesterol by 0.26 mmol/l, HDL cholesterol by 0.02 mmol/l, triglycerides by 0.05 mmol/l and the total cholesterol/HDL cholesterol ratio by 0.175, which theoretically corresponds to a coronary heart disease risk reduction of 9.1%. A pooled analysis of 11 cohort studies showed that replacement of 5 en% SAFA by (n-3 and n-6) PUFA was associated with a significant 13% reduction in coronary events and a 26% reduction in coronary heart disease mortality. These results are consistent with a meta-analysis of RCTs, which showed that replacing 5 en% SAFA by (n-3 and n-6) PUFA reduced coronary heart disease risk by 10%. These results have been interpreted as providing strong concordant evidence to support current recommendations to replace SAFA with the n-6 PUFA linoleic acid, and were recently translated into an American Heart Association (AHA) advice, to consume ‘at least 5 to 10 % of energy as n-6 PUFA’. Importantly, however, neither of these pooled analyses made a clear distinction between n-6 and n-3 PUFA species, and the Mozaffarian et al. meta-analysis of RCTs did not consider the potential confounding role of trans-fatty acids. The n-3 PUFA and trans-fatty acids have been positively and negatively related to CVD development, respectively. If distinction is made between interventions that selectively replaced SAFA and trans-fatty acids with n-6 PUFA/linoleic acid, and those that substantially increased both n-3 and n-6 PUFAs, a whole different picture emerges. Linoleic acid selective PUFA interventions produced no indication of benefit but rather a fairly consistent, but non-significant, signal toward increased risk of coronary heart disease and death.
These potentially negative effects of n-6 PUFA acid may even have been underestimated, since PUFA also replaced trans-fatty acids. If SAFA is replaced by both n-3 and n-6 PUFA, a significant (22%) decreased coronary heart disease risk is found. However, this reduction may also be attributable, at least in part, to the reduced consumption of trans-fatty acids. 34

RISK REDUCTION IN PERSPECTIVE

Besides the already mentioned large variability in the relationship between total cholesterol and SAFA intake,6 there is the well-known example of the African Maasai who had very high intakes of both cholesterol (500 to 2000 mg/day) and SAFA from milk,35,36 but exhibited remarkably low serum cholesterol levels8,11,35,36 and although accompanied by extensive atherosclerosis, with lipid infiltration and fibrous changes, they had a very low incidence of cardiovascular events.8 Secondly, comparison with other risk factors and the feasibility of a reduced SAFA consumption also require some attention. In 2003 the average SAFA intake in the Netherlands was estimated at 12.9% of total energy (en%). This intake should be lowered by 38%, i.e. to 7.9 en%, to achieve a 10% risk reduction in CVD.10 The Dutch National Institute for Public Health and the Environment (RIVM) calculated that a 5% reduction in SAFA intake would reduce the annual incidence of CVD by 4300 persons per year and CVD mortality by 1000 people per year,37 at an annual mortality from CVD of approximately 40,000/year in the Netherlands.38 For comparison, the estimated mortality attributable to overweight, insufficient fruit and vegetable intake, and low fish intake is 6900, 7300, and 4500 persons per year, respectively.37 A recent report from the UK predicted that an increase in the intake of fruits and vegetables from 279-356 g to 440 g/day would save as many lives as a reduction in the current SAFA consumption in the UK from >14 to 3 en% and a reduction in salt intake from >8.1 to 3.5 g/day.39 Consequently, other risk factors seem much simpler to be addressed and their role seems at least comparable, if not more important, in the current high incidence of CVD. Recommendations to increase intake of n-3 PUFA, fruit and vegetables and reduce sodium intake,40 to increase physical activity,40 to increase intake of n-3 PUFA, fruit and vegetables and the current high incidence of CVD. Recommendations role seems at least comparable, if not more important, in health.40 Moreover, there is convincing evidence that the LDL cholesterol reducing statins reduce CVD risk.41,42 Furthermore, it is well established that chronic systemic inflammation connects LDL cholesterol to CRP. There is increasing evidence that changes in serum lipoproteins might be a response to a state of chronic inflammation secondary to our current lifestyle that in turn is composed of many factors. Besides the influence of dietary changes, environmental changes such as stress, sleep deprivation and environmental pollution, including smoking, have also been related to chronic inflammation.43 It was recently re-emphasised that these so-called gene-environment interactions play important roles in de development of many, if not all, current diseases of civilization,44,45 while a primary role for ‘faulty’ genes, is grossly overestimated.46-53

Common metabolic disorders, such as obesity, type 2 diabetes and the metabolic syndrome, are associated with low-grade inflammation and elevations in acute phase proteins such as CRP.44 It has become increasingly clear that insulin resistance develops secondary to systemic inflammation and that the compensatory hyperinsulinaemia aims primarily at balancing glucose homeostasis.54-55 The insulin resistant state, induced by pro-inflammatory cytokines, is indispensable for the reallocation of energy-rich substrates. Glucose is conserved for the metabolically highly active brain and for the activated immune system, which both rely on glucose metabolism for their energy supply.55 Organs that would normally also use glucose become insulin resistant and use triglycerides and free fatty acids, distributed by the liver and adipose tissue, respectively, as energy sources. At the same time, the lipoprotein profile might act to fight off inflammation and support the repair of tissue damage secondary to the inflammatory reaction.56-66 This is executed via: 1) an increase in cholesterol-rich lipoproteins (mainly LDL and VLDL), which have the ability to bind bacterial lipopolysaccharide (LPS) in proportion to their cholesterol content.63,67,68 although the best determinant of the capacity of lipoprotein to bind LPS is a high phospholipid/cholesterol ratio (i.e. surface/volume ratio);69 2) the suppression of reverse cholesterol transport via multiple pathways66 (i.e. low HDL); 3) increased oxidation
of LDL and VLDL, while HDL becomes proinflammatory, 4) increased cholesterol delivery to the immune system, 5) the production of small dense LDL particles. The last-mentioned become enriched in sphingolipids, are poorly cleared by the LDL receptor, cross the endothelial barrier more effectively, bind to the vascular wall intima and are accumulated in macrophages because of their susceptibility to oxidative modification. 6) Taken together, the proatherogenic dyslipidaemia of the metabolic syndrome is in support of the recovery from inflammation-induced damage. However, when these changes in the lipoprotein profile last for prolonged periods of time, such as in the chronic low-grade inflammation of the metabolic syndrome, they give rise to the development of atherosclerosis.

Taken together that our current lifestyle includes many factors that i) initiate and propagate inflammation; 2) give rise to an inadequate capacity to terminate inflammatory responses; and 3) lead to insufficient protection from the collateral damage caused by the chronic immune activation. One of these factors is our dietary SAFA intake, which can cause inflammation by their mimicking of a part of bacterial LPS and/or by providing other pro-inflammatory stimuli. Whether dietary SAFA cause inflammation depends on the accumulation of SAFA in the body and not on the dietary SAFA intake per se. Accumulation of SAFA can also occur by the synthesis of SAFA from CHO via de novo fatty acid synthesis. This mainly occurs in the liver, which secretes these de novo synthesised fatty acids as VLDL.

SAFA VS CARBOHYDRATES, THE METABOLIC SYNDROME AND THE IMMUNE SYSTEM

The adverse effects of high SAFA intake on lipid metabolism are particularly noted when SAFA are combined with a high CHO intake. Under these conditions, dietary SAFA are preserved, while the surplus of the consumed CHO is converted to SAFA by hepatic de novo fatty acid synthesis. Although the conservation of SAFA during excessive intake of CHO with a high glycaemic index is well known, the synthesis of SAFA from (surplus) CHO may not have received sufficient attention. Contrary to widespread belief, de novo fatty acid synthesis is not restricted to hypercaloric conditions or to excessive intake of CHO, but also depends on the type of ingested CHO. A low-fat eucaloric diet with a high sugar/starch ratio stimulated de novo fatty acid synthesis and increased serum triglycerides in normal weight individuals. When subjects with the metabolic syndrome, i.e. with pre-existing insulin resistance, were fed either a hypocaloric low-CHO/high-fat diet with high SAFA content or a hypocaloric high-CHO/low-fat diet with low SAFA content, the low-CHO/high-SAFA diet resulted in lower SAFA levels in plasma lipids compared with the high-CHO/low-SAFA diet. Finally, in subjects with the hepatic manifestation of the metabolic syndrome, i.e. non-alcoholic fatty liver disease, 26% of the fatty acids in the liver triglycerides and 23% of the fatty acids in VLDL triglycerides derive from de novo fatty acid synthesis in the liver. Importantly, as much as 25 to 30% of Western adults are suffering from non-alcoholic fatty liver disease in which the hepatic synthesis of fat, including SAFA, has become independent of the metabolic state, i.e. is independent of the feeding-fasting cycle. Taken together, SAFA accumulate: 1) under eucaloric conditions in normal weight subjects who consume a CHO-rich diet with high glycaemic index; and 2) under hypocaloric conditions in subjects with the metabolic syndrome and non-alcoholic fatty liver disease who consume CHO-rich diets. Thus CHO, particularly those with a high glycaemic index, and pre-existing insulin resistance are confounding factors in the discussion on the relation between CVD and dietary SAFA. This observation underscores the importance of a renewed discussion about the possible dangers of dietary SAFA.

CONCLUSIONS

The total body of evidence suggests that attention should be shifted from the harmful effects of dietary SAFA per se, to the prevention of the accumulation of SAFA in body lipids. This shift would emphasise the importance of reducing dietary CHO, especially CHO with a high glycaemic index, rather than reducing dietary SAFA. The chronic interaction of SAFA with our immune system elicits so-called chronic systemic low-grade inflammation, which underlies the metabolic changes referred to as the (atherogenic) dyslipidaemia of the metabolic syndrome or the lipidaemia of sepsis. The ultimate goal of the ensuing insulin resistance is the re-allocation of energy-rich substrates, such as glucose, to the immune system while the change in our lipoprotein profile aims at the limitation of the inflammatory responses and the repair of the resulting tissue damage. Dietary SAFA belong to the many false triggers of inflammation that result from the conflict between our slowly adapting genome and our rapidly changing lifestyle, but among these many factors they are not the most important. A reduction in the consumption of CHO with a high glycaemic index, trans-fatty acids and linoleic acid, and an increased consumption of fish, vegetables and fruit, and a reduction of inactivity, sleep deprivation and chronic stress seem more realistic approaches to fight the current pandemic of cardiovascular disease resulting from chronic systemic low grade inflammation.

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Vancomycin nephrotoxicity: myths and facts

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ABSTRACT

Vancomycin is a key antibiotic in the management of severe Gram-positive infections. Recent emergence of methicillin-resistant staphylococcal strains with reduced susceptibility to vancomycin has prompted internists to administer high-dose treatment to achieve trough levels of 15 to 20 mg/l. Such high doses might be causative in nephrotoxicity. The risk further increases in patients who are critically ill and are on vasopressor support and/or concomitant nephrotoxic agents, with baseline deranged renal function, undergoing prolonged duration of therapy and are obese. However, data are insufficient to recommend the superiority of continuous infusion regimens as compared with intermittent dosing. This review discusses the literature pertaining to vancomycin nephrotoxicity.

KEYWORDS

Dose, nephrotoxicity, trough levels, vancomycin

INTRODUCTION

Vancomycin is a cornerstone antibiotic for the management of severe Gram-positive infections. Introduced into clinical practice in 1956, it is a bactericidal glycopeptide with a molecular weight of 1,446 Da. It inhibits the cell wall synthesis of Gram-positive bacteria by the formation of stable complex murein pentapeptides, thus causing inhibition of further peptidoglycan formation. The killing action of vancomycin is slow and is negatively affected by biofilm formation, stationary growth phase, large bacterial inoculates, and anaerobic growth conditions. Early batches of vancomycin contained significant impurities, leading to a variable toxicity and the nickname Mississippi mud. Subsequently, production of this antibiotic was revised so that preparations are absolutely free of these impurities.

The relationship between serum concentrations and treatment success or failure in serious Staphylococcus aureus infections has recently been established. The pharmacokinetic-pharmacodynamic (PK-PD) parameter best predicting activity of vancomycin against staphylococcal species is the 24-hour area under the concentrations curve over the minimal inhibitory concentration (AUC/MIC). On the basis of in vitro, animal and limited human data, an AUC/MIC value of 400 has been established as the PK-PD target. However, these values are hardly obtainable in S. aureus strains with a MIC of 2 μg/dl. Also, the calculation of AUC/MIC is not practically feasible. Trough levels have a good correlation with total drug exposure given by the AUC/MIC and are therefore recommended as the most precise and workable monitoring method in daily clinical practice. These trough levels should be obtained just before the fourth dose at steady state conditions.

MECHANISM OF VANCOMYCIN NEPHROTOXICITY

Elimination of vancomycin is almost exclusively renal. Vancomycin is renally eliminated mainly via glomerular filtration, and to some extent via active tubular secretion. Animal studies have suggested proximal renal tubular cell necrosis by vancomycin accumulation as mechanism of nephrotoxicity. Vancomycin-induced renal damage requires energy-dependent transport from the blood to the tubular cells across the basolateral membrane. In the tubular cells, vancomycin presents a pronounced lysosomal tropism. Animal studies suggested oxidative stress might underlie the pathogenesis of vancomycin-induced toxicity. Gene expression analyses in mice have suggested involvement of oxidative stress and mitochondrial damage in vancomycin-induced kidney injury. More importantly, a potential contribution of complement pathway and inflammation in the vancomycin-induced renal toxicity has been observed.
postulated. In addition to necrosis, signs of tissue repair were also detected in vancomycin-treated animals. Severe vancomycin renal toxicity may present histologically as tubulointerstitial nephritis, sometimes with granulomas. Apparently, in rats, curcumin ameliorated vancomycin-induced decrease in the activities of antioxidant enzymes and glutathione peroxidase and could be able to antagonise vancomycin nephrotoxicity. A protective and antioxidant effect of vitamin E, vitamin C, N-acetylcycteine, caffeic acid phenyl ester, and erythopoeitin on vancomycin-induced nephrotoxicity in rats has also been reported. Whether antioxidant therapy is protective against vancomycin-induced nephrotoxicity in humans remains to be established.

Approximately 5 to 8.5% of vancomycin clearance is extrarenal, possibly by hepatic conjugation, leading to vancomycin crystalline degeneration products. The clearance decreases with creatinine clearance in a linear fashion, resulting in markedly increased half-life of 100 to 200 hours in anuric patients.

**STAPHYLOCOCCI SUSCEPTIBILITY AND VANCOMYCIN TROUGH LEVELS**

In 2006, the Clinical and Laboratory Standard Institute established breakpoints for vancomycin for *S. aureus*. A MIC ≤2 μg/ml is defined as susceptible, a MIC of 4 to 8 μg/ml is intermediary susceptible and a MIC ≥16 μg/ml as resistant (*vancomycin-resistant S. aureus* or VRSA). VRSA have acquired vanA gene from vancomycin-resistant enterococci, leading to altered murein pentapeptide target with strongly decreased binding affinity for vancomycin and thus a high level vancomycin resistance with MIC >32 μg/ml. Within the group of susceptible *S. aureus*, the proportion of staphylococci with a MIC for vancomycin between 1 to 2 μg/ml is steadily increasing, indicating a further shift of MIC to the right. Staphylococci with a MIC between 1 to 2 μg/ml pose a higher risk for treatment failure than more susceptible species.

**VANCOMYCIN NEPHROTOXICITY - LITERATURE REVIEW (TABLE 1)**

A computerised literature search of PubMed for all relevant data was done using the terminology “vancomycin nephrotoxicity”. High dose was defined as either a daily dose of ≥4g or >30 mg/kg or regimens that achieved serum vancomycin trough concentrations of 15 to 20 mg/l. Nephrotoxicity was defined as ≥50% increase in serum creatinine (SCR) from baseline value or a 50% decrease in creatinine clearance (CCl) from baseline. The majority of studies were retrospective in design.

This definition of vancomycin-induced nephrotoxicity has been accepted by the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists consensus statement with the rider that multiple (at least two or three consecutive) high serum concentrations should be documented after several days of therapy in the absence of an alternative explanation.

**INCIDENCE OF NEPHROTOXICITY**

The incidence of vancomycin-induced nephrotoxicity is variable ranging from <1% to >40% in various studies. The variability is due to the baseline population studied, different dosing regimes, and under-reporting of nephrotoxicity. Many of the studies did not target adverse events as their endpoints.

**TROUGH LEVELS AND NEPHROTOXICITY**

Lodise et al. identified vancomycin trough level as the pharmacodynamic parameter that best describes the relationship between exposure and toxicity. In retrospective analysis of 166 patients (27 high dose, 139 standard dose), AUC and trough levels obtained within 96 hours of therapy were modelled as continuous, dichotomous and categorical variables to describe the relationship...
between drug exposure and toxicity. A multivariate logistic regression yielded an adjusted odds ratio of 1.13 for an increased likelihood of nephrotoxicity with each one-unit rise in the initial vancomycin trough value (95% confidence interval (CI) 1.05 to 1.21; p=0.001).³

Ten studies have identified elevated vancomycin trough level (>15mg/l) as a significant predictor of nephrotoxicity, with an overall incidence of 27% for trough exposure of 15 to 20 mg/l; all studies included patients with other known causes of acute kidney injury (AKI), comprising concomitant receipt of nephrotoxins.⁵⁻¹⁴ For patients who achieved a trough level of >20 mg/l, the reported incidence rates were 21%, 33%,³³ 31%³¹ and 65%.¹⁸ However, it was not clear whether the trough level of >20 mg/l was measured after the onset of nephrotoxicity in the above studies. Thus, the elevated levels may represent the effect rather than the cause of nephrotoxicity. Moreover, the temporal relationship between elevated trough concentrations and development of nephrotoxicity is unclear in most studies, leaving a gray zone regarding a cause-effect relationship. Additionally, whether trough levels represent a steady-state value is also uncertain from most studies. In a small study, where trough levels were measured prior to the onset of nephrotoxicity, all eight patients without concomitant risk factors who attained trough levels of >20 mg/l had nephrotoxicity.²⁰

Observational data analysing vancomycin doses and nephrotoxicity are compromised by the presence of a selection bias.¹⁸,¹⁹ Patients with a greater severity of illness and an increased baseline risk of nephrotoxicity are more likely to receive aggressive vancomycin dosing regimes. Selection biases make the previous studies inadequate to accurately identify the rate of nephrotoxicity with higher vancomycin dosing. This is in agreement with the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Disease Pharmacists consensus statement acknowledging that there are limited data to suggest a direct causal relationship between nephrotoxicity and a specific vancomycin concentration.¹

**ONSET, DEGREE AND RESOLUTION OF NEPHROTOXICITY**

The onset of nephrotoxicity ranges from four to eight days from the start of therapy.³⁹,⁴⁰,⁴¹ It is of considerable importance to understand the fact that SCR is insensitive to detect mild changes in renal functions and the exact relationship between vancomycin exposure and onset of nephrotoxicity cannot be precisely determined based on changes in SCR values. Perhaps, urinary and/or serum biomarkers of AKI might help in future to solve this question.

The resolution of nephrotoxicity was seen in 71% (50% while on vancomycin therapy and 21% within 72 hours of discontinuation) in one study.²² In another study, 72.5% of patients had a return of SCR to their baseline value at the time of discharge and none of their study patients required renal replacement therapy as a consequence of nephrotoxicity.¹⁸ Nephrotoxicity resolved in 81% (17/21) of cases evaluated in a retrospective study.²⁴

**RISK FACTORS FOR VANCOMYCIN NEPHROTOXICITY (FIGURE 1)**

In retrospective data from various studies, in total 307 patients were evaluated. Nephrotoxicity occurred in 6.6% of patients on high-dose therapy compared with 2% in patients on standard-dose therapy in absence of concomitant risk factors for nephrotoxicity.¹⁷⁻¹⁹ In one study where primary analysis was on patients without concomitant nephrotoxicity risk, minimal increases in SCR values from baseline were seen for the high-dose group (88.4 to 97.2 μmol/l), whilst SCR values remained unchanged in the standard-dose group.²⁵

In studies from intensive care units (ICU), various concomitant risk factors confound the analysis when comparing vancomycin exposure and nephrotoxicity. However, a high Acute Physiology and Chronic Health Evaluation II score,¹⁸,²¹ ICU residence,²¹ and receipt...
of vasopressor agents appear to be significant risk factors for the development of nephrotoxicity. Lodise et al. observed that ICU patients have a higher baseline risk for development of nephrotoxicity than non-ICU patients at a lower trough concentration threshold: >20% probability of nephrotoxicity at a trough >10 mg/l in ICU patients versus trough >20 mg/l in non-ICU patients. Obesity was seen to be a significant predictor for occurrence and time of development of nephrotoxicity. The authors postulated that dosing from total (including fat) mass will increase the dose if dosing is weight based and, therefore, increase the vancomycin AUC, thus shortening the time to event. Also, the volume of distribution in the central compartment (V) did not increase proportionally with weight and that V accounted for the higher trough values observed among obese patients in their study.

Sepsis and duration of therapy were other factors more likely to be associated with development of nephrotoxicity. Prabaker et al. observed that the rate of nephrotoxicity increased from 12 to 22% beyond ten days of therapy. Jeffres et al. observed an odds ratio of 2.55 for nephrotoxicity after ≥14 days of treatment. In another study, Hidayat et al. found that the risk appeared to increase incrementally as the treatment was prolonged in patients who achieved high trough levels (15 to 20 mg/l): 6% for ≤7 days, 21% for 8 to 14 days and 30% for >14 days. A recent two-phase retrospective analysis identified vancomycin serum trough concentrations ≥14 mg/l, duration of vancomycin therapy ≥7 days, and baseline SCR levels ≥1.7 mg/dl as independent predictors of nephrotoxicity. The use of concomitant nephrotoxins appears to be a significant risk factor for development of nephrotoxicity. However, most studies did not specify the number of concomitant nephrotoxins and none reported the duration of concomitant nephrotoxic exposure during vancomycin therapy. In a recent retrospective analysis in a paediatric population, nephrotoxicity occurred in 14% of the population especially in those with targeted troughs ≥15 mg/l, in the intensive care unit, and receiving furosemide. Furosemide is not a direct nephrotoxin, but its use may cause dehydration, in which the addition of vancomycin may further increase the risk of developing nephrotoxicity. Another study showed that a loop diuretic was present in 63% of adult patients who had nephrotoxicity during vancomycin therapy as compared with 44% with no renal toxicity (p=0.083).

Continuous infusion was associated with slower onset of nephrotoxicity. However, the ultimate prevalence of nephrotoxicity was identical and associated with cumulative vancomycin exposure. Furthermore, in a retrospective cohort study, Hutschala et al. showed a tendency for less nephrotoxicity with continuous infusion compared with intermittent infusion of vancomycin in critically ill patients after cardiac surgery. But, there was no significant difference in the requirement of continuous veno-venous haemofiltration amongst the groups and the intermittent administration group tended to have higher baseline SCR values. In a prospective study, Vuagnat et al. showed that continuous vancomycin infusion was logistically more convenient, achieved target concentrations faster, resulted in less variability in serum vancomycin concentrations, required less therapeutic drug monitoring and caused less adverse effects, but the clinical superiority was not established. The consensus guidelines recommend that continuous infusion regimens are unlikely to substantially improve patient outcomes, compared with intermittent dosing. Data on comparative vancomycin toxicity for continuous versus intermittent administration are conflicting and no recommendations can be made.

**OTHER TOXICITIES**

Historically, the most common vancomycin toxicity was the red man syndrome. It is an acute hypersensitivity reaction, consisting of flushing and pruritus, occasionally accompanied by hypotension. The onset may occur within a few minutes and usually resolves over several hours, after completion of the infusion. Patients usually tolerate subsequent doses if the dilution and the period of infusion are increased.

Another adverse effect is ototoxicity, the overall incidence of which appears to be low. Despite clinical case reports of a relationship between vancomycin serum concentrations and ototoxicity, there are no animal models that have demonstrated this relationship. The majority of experts feel that this drug is not ototoxic.

Other side effects include neutropenia, fever, phlebitis, thrombocytopenia, lacrimation, linear IgA bullous dermatosis, necrotising cutaneous vasculitis, toxic epidermal necrolysis and Stevens-Johnson syndrome.

**CONCLUSIONS**

Vancomycin nephrotoxicity is an important clinical adverse outcome to one of the commonly used antibiotics in modern-age medicine practice. It is unclear from the studies whether this is a result of targeting higher drug levels or a result of use in patients who have significant
AKI, especially in the ICU setting. There is lack of evidence and a myth that this is solely due to one of the above factors and it may very well be a combination of both. Clinicians are targeting trough levels of 15 to 20 mg/l. There is difficulty in discerning whether vancomycin levels are a cause of nephrotoxicity or are raised secondarily to nephrotoxicity. Physicians have to be aware of this entity while managing patients who are treated with this antibiotic and one needs to remember one of the important pillars of our decision making ‘to do no harm’ while managing these sick individuals.

Timely detection of this clinical adverse outcome and discontinuation or replacement with other antibiotics has shown to prevent long-term kidney damage. That acute vancomycin nephrotoxicity leads to chronic kidney damage is a myth, unfounded, as per current literature. One must also be aware of concomitant nephrotoxins which contribute to this phenomenon and these should be avoided. Until molecular/biomarkers of AKI become available, cautious use of vancomycin is justified. Nevertheless, the patient should not be deprived of the benefits of this magic bullet, at least, in the critically ill stages.

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Identification of patients with upper gastrointestinal bleeding who do not need immediate treatment

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KEYWORDS
Upper gastrointestinal bleeding, acute gastrointestinal bleeding, Glasgow Blatchford Bleeding Score

INTRODUCTION

Background
With estimates of the population-based incidence of between 48 and 134 per 100,000 adults per year, acute upper gastrointestinal bleeding can be considered a common reason to visit emergency departments (ED).4 Reported mortality rates for such patients range from 5% to 14% in different studies.3-7 The presentation of patients with upper gastrointestinal bleeding varies from clinically insignificant bleeding to hypovolaemic shock. Depending on the nature of the bleeding, some of these patients do not need immediate treatment because the bleeding will stop spontaneously with little risk of clinical complications or rebleeding. These patients could be further treated as outpatients. However, because the cause of the bleeding cannot be determined from the clinical presentation and emergency endoscopy is not readily available in the ED, it is common practice to admit patients for observation and endoscopy.

Clinical characteristics and the cause of the bleeding as diagnosed with endoscopy are highly predictive of adverse outcomes such as rebleeding and mortality.3 Quantification of clinical severity with a dedicated score could be a useful tool toward a more objective determination of the need for immediate intervention. Several scoring systems have been developed to stratify patients with acute upper gastrointestinal bleeding according to prognosis.3-12 The Rockall score is such a risk stratification tool that is based on clinical and endoscopic findings.14 In 2000 the Glasgow Blatchford bleeding Scale (GBS) was developed. The GBS is a screening tool to assess the likelihood that a patient with acute upper gastrointestinal bleeding will need medical intervention (e.g. blood transfusion, endoscopic or surgical treatment) only based on patient history, clinical examination and laboratory tests. Advantages of the GBS include absence of highly subjective variables (e.g. severity of systemic diseases) and the fact that there is no need for endoscopy.9 The Haemoglobin-Urea-Pulse-Systolic blood pressure (HUPS) score is a simplified fast-track risk screening tool that only uses the clinical and laboratory data of the GBS.8 According to the original article it should only be used when patients have no major comorbidity. GBS and HUPS scores are unique because they can easily be determined in the ED.

Several studies have shown that the GBS score can identify patients who can be safely sent home without any endoscopic intervention.12-14 In the initial study, patients with a GBS score of 0 were classified as low risk for the need of clinical intervention. Later studies showed that a cut-off value of 2 still reliably identified patients with no need for immediate intervention.1,9,10,13-15 The GBS has not yet been evaluated for use in the Netherlands. The aim of the present study was to validate the GBS scale in the Netherlands and to determine the cut-off value for safely treating patients as outpatients. A further aim was to compare the GBS scale system with the HUPS score and the Rockall score as to their ability to predict absence of the need for immediate treatment.

MATERIALS AND METHODS

Study design and setting
This historical cohort study was performed in the Maastricht University Medical Centre (MUMC). Each year about 22,750 patients visit the ED of whom 5075 patients present to internal medicine or gastroenterology. About
200 of these patients are investigated under the diagnosis of acute upper gastrointestinal bleeding. Endoscopy, mainly performed in the endoscopy department, was available 24 hours a day, seven days a week. The study was conducted with the approval of the medical ethical committee of MUMC.

Study population
We retrospectively reviewed the charts of all patients admitted to the ED for suspected acute upper gastrointestinal bleeding in the following period: 1 July 2009 and 31 January 2010. Patients had to fulfil all of the following inclusion criteria: 1) presentation at ED with haeamatemesis, melaena, tarry stool or syncope with anaemia; 2) diagnosis of acute upper gastrointestinal bleeding was included in the working differential diagnosis formulated by the internist or gastroenterologist; and 3) age over 18 years. Patients with signs of chronic bleeding (microcytic anaemia) were excluded. In contrast to other studies we did not include patients who developed acute upper gastrointestinal bleeding while hospitalised for other reasons.

Data collection/methods of measurement
Data were collected using the ED files and the electronic database of the hospital. To check completeness of obtained data, the reports of all gastroduodenal endoscopies performed in the research period were screened as well. The abstraction of the charts was performed by a research student, who was not blinded for the study hypothesis. All patients were discussed with a gastroenterologist (YK). The following data were collected: date of admission to the ED, symptoms and signs of the gastrointestinal bleeding, haemodynamic variables (pulse and systolic blood pressure), laboratory results (serum haemoglobin and urea concentrations), demographic information, current medication, comorbidity, length of in-hospital stay, moment (inpatient or outpatient) and findings of endoscopy.

As comorbidities we recorded hepatic disease/failure, kidney disease/failure, cardiac failure, and disseminated malignancy. Used medication was retrieved from the ED chart with special attention for the following medication: proton pump inhibitors, carbasalate calcium, antiocoagulants, H2 antagonists, non-steroidal anti-inflammatory medication or corticosteroids. If items were not mentioned in either the ED chart or the electronic database we considered them to be negative.

We calculated the Glasgow Blatchford (table 1), HUPS and Rockall scores of the patients based on the collected data. Need for treatment during the period of 28 days following presentation was considered to be present when, in this period, treatment (e.g. blood transfusion, surgical, radiological or endoscopic intervention) was actually performed, when rebleeding requiring readmission occurred, or when the patient died. Information about readmission, rebleeding or death was gathered from the charts and/or general practitioner.

Data processing and sensitivity analysis
Statistical analysis was performed using SPSS 15.0. Data are presented as means with standard deviation (SD) and proportions where appropriate with exact 95% confidence intervals (CI). We calculated areas under the receiver-operating curves with 95% CI as estimates of the discriminatory ability of the scoring tool. Sensitivity and specificity of dichotomised scores at usual cut-off levels were calculated to guide the choice for a proper cut-off level. Likelihood ratios for individual scores were calculated to estimate the diagnostic information associated with each score. We refrained from statistical testing because of the exploratory nature of the study.

RESULTS
Characteristics and management of patients with acute upper gastrointestinal bleeding
A total of 103 patients with acute upper gastrointestinal bleeding were enrolled in this study. Table 2 outlines the demographic characteristics and outcomes for these patients. Eighty-one (79%) underwent endoscopy. A total of 11 patients (10.7%) suffered from rebleeding in the
follow-up period; also 11 patients (10.7%) died during the follow-up period.

Table 3 shows the endoscopic findings of these patients. For 11 patients (11%) it was not possible to calculate the GBS and HUPS scores because some of the haemodynamic or laboratory variables were missing. In 24 patients (23%) the Rockall score could not be calculated because endoscopy had not been performed.

Table 4 shows the likelihood ratios for the different values of the GBS in the validation group of the original study population (Blatchford validation group) and in our patient group. Receiver-operating characteristic analysis showed very good discriminative ability with an area under the curve (AUC) of 0.94 (95% CI 0.90 - 0.98) (figure 1).

Four patients (4%) had a GBS score of 0, while 17 (18%) of patients had a score below 2. In the 28-day follow-up period, none of these patients needed treatment. For a cut-off value of 0, sensitivity and specificity for the need of treatment were 100% (95% CI 95 to 100%) and 12% (95% CI 4 to 26%) respectively. With a cut-off value of 2 the sensitivity was still 100% (95% CI 95 to 100%), while the specificity increased to 51% (95% CI 35 to 67%).

Comparison of the three different risk scoring systems

Using the cut-off value of ≥2 points as suggested in the original study, the Rockall score classified 21 patients (26.6%) at low risk of needing treatment (figure 2). However, of these 21, four patients met the study definition of needing clinical intervention: three patients received blood transfusion and one patient needed an endoscopic...
intervention. The HUPS score identified 14 patients (15.2%) with score 0. None of these patients needed intervention (figure 2). We compared the ROC curves of the three scoring systems for the patient group in which all three scores could be calculated. With an AUC of 0.94 (CI 0.89 to 0.99), the GBS proved to be superior to the HUPS score and the complete Rockall score with AUCs of 0.85 (CI 0.75 to 0.95) and 0.88 (CI 0.79 to 0.96).

**DISCUSSION**

In this study we validated the Glasgow Blatchford bleeding scale in the setting of a Dutch university hospital. The GBS showed to have good discriminative ability to distinguish acute upper gastrointestinal bleeding patients who do and who do not need intervention in the ED. The area under the ROC curve was 0.94 (95% CI 0.90 - 0.98) which is similar to the AUC in the original validation group of Blatchford et al.: 0.92 (95% CI 0.88 to 0.95). Diagnostic information per individual GBS expressed as likelihood ratios showed roughly the same trend in the original validation group and in our study. However, it is evident that a much larger study will be needed to reliably estimate the likelihood ratios and make valid comparisons between groups.

The cut-off value between low or high risk of needing treatment was set at 0 in the original study.9 In this way a sensitivity of 98.9% was reached. In our group, 4% of patients had a score of zero with a sensitivity of 100%. Previous studies found a higher percentage of patients with a score of 0, ranging from 8 to 17%.9,17 Stanley et al. used the cut-off value of 0 and identified 123 patients (22%) as low risk and managed 84 (17%) of them as outpatients.15

In our study a higher cut-off value of 2 still had a sensitivity of 100%. Therefore, the 18% of the patients with this score could have been safely managed as outpatients. Previous studies also indicated that a cut-off value of 2 should be safe. Stephens et al. used the combination GBS <2 and age younger than 70 years as a criterion, because they believed that it was not safe to treat the elderly as

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outpatients. They found that this way 10% of their patients with acute upper gastrointestinal bleeding could be safely managed without hospital admittance.\textsuperscript{7} Srirajaskanthan \textit{et al.} identified 64 patients (38.6%) who had a GBS score of <2, all of whom could be safely managed as outpatients.\textsuperscript{1} The Rockall score was originally developed to predict the risk of death and rebleeding.\textsuperscript{12} To prevent such events it is clear that one should be able to identify those patients who need treatment. Therefore, in practical terms the Rockall score has the same purpose as the other two scoring instruments. Until now the HUPS score has not been externally validated.

Our study shows that in our population, the discriminative ability of the GBS score was superior to the complete Rockall score and the HUPS score. Earlier reports also indicated that the GBS is better than the complete Rockall score.\textsuperscript{9,10,15,16} The inferior performance of the HUPS score can possibly be attributed to the fact that it is only considered to be useful in the absence of other major pathology.

There were several differences between our study and earlier studies in this field. Unlike other studies we did not exclude patients with bleeding varicose veins and patients without endoscopy in the follow-up. We did that because the purpose of the risk scoring tools is to support clinical decision making in the absence of endoscopic findings. We did not include patients who developed acute upper gastrointestinal bleeding while admitted to the hospital because they are not seen in the ED and are not representative of the acute upper gastrointestinal bleeding patients who come to the ED. Also, we used the 28-day mortality and rebleeding and not only in-hospital events because we also included patients who were primarily treated as outpatients.

A limitation of our study is the use of retrospective data collection from hospital files. We were therefore dependent on the completeness of the medical chart. It is possible that we missed some relevant information. For 11% of the patients we were not able to collect all the data that were needed to calculate the GBS and HUPS scores. However, the main limitation of the study is its small size. Before introduction of the GBS score for clinical purposes the study should be repeated in a much larger population and preferably with prospective data collection.

The GBS and HUPS scoring systems are unique because they do not require endoscopy, and therefore they can easily be used at the ED. With a cut-off value of 2, an appreciable number of patients can be identified for whom treatment as outpatients is preferable. This would result in a reduction of hospital days, more adequate and efficient patient care and lower healthcare costs. It is reassuring that, despite differences in the composition of patient populations, the GBS seems to perform equally well in the Netherlands as in its original validation study and other studies.

In conclusion, the GBS score appears to be a good predictor of the need for treatment in a Dutch ED population of patients with acute upper gastrointestinal bleeding. It was superior to the often used complete Rockall and HUPS scores. Larger studies are needed to substantiate the conclusions.

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A case of hyperammonaemic encephalopathy due to valproic acid

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ABSTRACT

A patient with valproic acid induced hyperammonaemic encephalopathy is presented. During chronic treatment with valproic acid this patient developed a potentially life-threatening encephalopathy without signs of liver failure. After discontinuing the valproic acid the patient recovered completely. In the case of a patient presenting with hyperammonaemic encephalopathy, the possibility of the use of valproic acid should not be overlooked.

KEYWORDS

Hyperammonemic encephalopathy, valproic acid

INTRODUCTION

We present a case with an unusual cause of hyperammonaemia without signs of liver failure. The patient presented with lethargy and apnoeas and was on chronic valproic acid therapy. After the valproic acid was discontinued, the patient recovered completely. Our diagnosis is a valproic acid induced hyperammonaemic encephalopathy (VHE). Hyperammonaemic encephalopathy is a relatively rare side effect of valproic acid therapy and most case reports describe hyperammonaemic encephalopathy after initiating valproic acid therapy. This case illustrates that life-threatening hyperammonaemic encephalopathy can occur in chronic therapy with valproic acid and without liver failure. If a patient presents with signs of encephalopathy and the use of valproic acid, the ammonia should be checked and valproic acid should be discontinued.

CASE REPORT

A 57-year-old male was brought to the emergency department because of unconsciousness. His medical history revealed alcohol intoxication and epilepsy. The epilepsy was due to intracranial surgery eight years ago because of a traumatic intracerebral haematoma. His list of medication showed the use of 400 mg carbamazepine twice daily and 1500 mg valproic acid three times daily. Because of the somnolence no further history could be obtained. No further information was available at that point.

On physical examination the blood pressure was 97/62 mmHg, temperature 35.1 °C, and the Glasgow Coma Scale was 13 (E3M6V4). He had a flapping tremor. Physical examination was otherwise unremarkable. CT scan of the cerebrum showed no new lesions. Laboratory tests revealed marked levels of γ-glutamyl transferase (144 U/l, normal <45 U/l) and marked ammonia levels (132 μmol/l, normal 9 to 33 μmol/l), alcohol was undetectable. Other liver enzymes and parameters for synthesis function of the liver were in the normal range.
A metabolic encephalopathy was suspected. Because of the apnoeic episodes the patient was admitted to the intensive care unit for observation. He received oxygen, thiamine and lactulose. All antiepileptic drugs were discontinued. In the next six hours the patient regained full consciousness and his physical parameters were stable. Valproic acid levels were revealed to be toxic (168 mg/l, therapeutic range 50 to 100 mg/l).

After discontinuing the lactulose, the ammonia levels remained normal and stable. The patient recovered completely. An ultrasound of the abdomen and endoscopy showed no signs compatible with liver cirrhosis. Our diagnosis is a hyperammonaemic encephalopathy due to valproic acid, a phenomenon which is described in a number of case reports. The cause that led to the hyperammonaemic encephalopathy remains unrevealed. According to our patient he had taken his medication as prescribed and there had been no alterations in his diet.

DISCUSSION

In this case the patient presented with the clinical features of a metabolic encephalopathy, a hyperammonaemia without liver failure and a toxic level of valproic acid during the chronic use of valproic acid. After discontinuation of valproic acid, his symptoms were relieved and the ammonia and valproic acid levels returned to normal. This suggests a causal relationship between the hyperammonaemic encephalopathy and valproic acid. Hyperammonaemic encephalopathy due to the chronic use of valproic acid in the absence of liver failure is relatively unknown and a serious complication of the use of valproic acid. There are several case reports on VHE due to acute overdose of valproic acid, but only a few case reports on VHE due to the chronic use of valproic acid.¹⁻⁵

CLINICAL FEATURES

Clinical features of VHE are mild to moderate lethargy, increased seizure frequency with progress to stupor and coma.⁴ In chronic valproic acid therapy onset can be insidious.¹ Combination with other antiepileptic drugs such as carbamazepine can potentiate the toxic effect.⁹

HYPERAMMONAEMIC ENCEPHALOPATHY

Hyperammonaemic encephalopathy occurs in acute overdose and in chronic therapy with valproic acid and is not dose related.¹⁵ Asymptomatic hyperammonaemia is seen in 20 to 25% of the users of valproic acid.⁶ The daily dosage of valproic acid and the levels of valproic acid and ammonia are not related to the degree of encephalopathy.⁴ Several mechanisms for the development of hyperammonaemic encephalopathy in valproic acid therapy have been proposed. Changes in dietary protein intake may affect serum ammonia levels. Valproic acid stimulates the production of ammonia in the kidney.⁷ Valproic acid is partly metabolised in the liver by oxidation which produces active metabolites. These metabolites inhibit enzymes in the liver (mitochondrial carbamyl phosphate synthetase) necessary for ammonia elimination via the urea cycle.⁴ In chronic valproic acid therapy the amount of oxidation and the production of active metabolites increases.⁶ Additionally, chronic valproic acid therapy depletes carnitine, an essential substrate for the metabolism of valproic acid. Depletion can result in a reduced capacity of the ammonia metabolism.⁴⁻⁹

Inborn errors in the urea cycle can also result in hyperammonaemic encephalopathy. Ornithine-transcarbamylase (OTC) deficiency is the most common inherited urea cycle disorder and is X-linked. Affected men usually die young due to an impaired ammonia metabolism. Heterozygote women can be asymptomatic and valproic acid may induce a symptomatic hyperammonia.¹,⁵,¹¹ In our patient we found an OTC deficiency very unlikely and did not evaluate this, since he had taken valproic acid for a long time without symptomatic hyperammonia. In addition affected men with an OTC deficiency seldom present at this age. In women presenting with a hyperammonia, however, one should rule out an OTC deficiency. A low clearance of citrulline in urine or an allopurinol test can be of diagnostic use.¹⁰,¹¹

The pathogenesis of encephalopathy due to hyperammonaemia in valproic acid therapy remains unrevealed. It is suggested that due to high cerebral levels of ammonia, production of glutamine increases and glutamine excretion is inhibited in the astrocytes, what leads to the swelling of astrocytes and cerebral oedema.⁴⁻²² Also, increase in the activation of gamma-aminobutyric acid (GABA) by ammonia induces somnolence.⁴⁻⁹

CASE REPORTS

We found five cases of long-term treatment with valproic acid and the development of hyperammonaemic encephalopathy.¹,³,⁶,¹¹,¹² All five cases report altered mental status, stupor or lethargy due to hyperammonaemia and without signs of liver failure. Duration of valproic acid therapy varied from 3 to 11 years. In three of the five cases there was concomitant use of antiepileptic drugs. The ammonia levels measured ranged from 83 to 377 μmol/l, valproic acid levels were within the therapeutic range in all cases, ranging from 48 to 101 μg/ml. Symptoms were relieved after discontinuing valproic acid and prescribing lactulose. In one case report L-carnitine was supplemented.¹³ The immediate cause of the VHE remained unrevealed in all five cases.
Our findings are consistent with the cases described above. Only we found a toxic level of valproic acid. The time of ingestion of the valproic acid is unknown in our case. The level measured could have been a peak level after ingestion (1 to 4 hours). We suggest that the cause of VHE is multifactorial, as is outlined above: due to change in dietary protein intake, increase in active metabolites in chronic valproic acid therapy and the combination of other antiepileptic drugs. Also non-adherence of the patient remains a possibility.

CONCLUSION

Hyperammonaemic encephalopathy is a rare and serious side effect of valproic acid and can occur without liver failure. Unlike most case reports this case of VHE occurred during chronic therapy with valproic acid. The cause remains unclear, though we suggest that the combination of risk factors might have potentiated the risk of VHE. In the case of a patient taking valproic acid and presenting with encephalopathy, regardless of the duration of therapy, ammonia levels should be checked and the valproic acid should be discontinued.

REFERENCES

Analysing completion times in an academic emergency department: coordination of care is the weakest link

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ABSTRACT

Congestion with prolonged stay in the emergency department (ED) is associated with poor health outcomes. Many factors contribute to ED congestion. This study investigates the length of time spent in the ED (time to completion) and the factors contributing to prolonged stay in an academic ED. Data of ED patients were prospectively collected during four weeks in February 2010. Presentation time, referrer, discharge destination, and medical specialities involved were registered in 2510 patients. Additional detailed data about relevant time steps were collected from 66 patients in the triage category Emergency Severity Index (ESI) 3. The Pearson’s chi-square test and the Mann-Whitney test were used for statistical analysis. Time to completion was longer than four hours in 13% of patients (average in total population 2:23 hours). In ESI 3 patients, 24% stayed longer than four hours in the ED (p<0.001). Internal medicine had most patients exceeding the four-hour target (37%), followed by neurology (29%). Undergoing a CT scan, treatment by multiple specialities, age above 65 years and hospital admission were associated with exceeding the four-hour target (p<0.001). The elapsed time between receiving test results and admission/discharge also influenced the completion time (p<0.001). A significant percentage of vulnerable and ill patients with triage category ESI 3 exceeded the four-hour completion time in our ED. Absence of coordination of care when multiple specialists were involved and delay in the process of decision-making after completion of all diagnostics on the ED were among other factors responsible for this prolonged stay. Improving the coordination of care will, in our opinion, speed up the decision-making process and lead to shortening of completion times in many patients.

KEYWORDS

Completion time, decision-making, emergency department, four-hour target length of stay.

INTRODUCTION

In the past, increased congestion with long waiting times in emergency departments (EDs) in the United Kingdom (UK) was frequently noticed. With the aim of reducing this congestion, the National Health Service in the UK set a target which prescribed that all patients presenting at the ED should be examined, treated, admitted or discharged (time to completion) in less than four hours. This resulted in a tremendous improvement in the time to completion. Although congestion with long waiting times is frequently noticed in some EDs in the Netherlands, no target for time to completion is defined or enforced. In our opinion, it is preferable to keep the length of stay at the ED short, in order to transfer patients to a stable and a safe environment as soon as possible. It has been demonstrated that the length of stay at the ED is associated with high risk of morbidity and mortality, preventable medical errors, poor pain control, longer hospital stay and decreased patient satisfaction. At the VU University Medical Centre (VUMc) Amsterdam, an academic tertiary care centre, it was noticed that in the past years the time to completion exceeded four hours in many patients. However, reasons for these delays were unclear and the exact percentage of patients spending more than four hours in the ED was unknown.

Therefore, in November 2009 we started a project to analyse ED congestion. The primary goal of this study was to measure the time to completion of the patients
Presenting at the ED and to detect which factors and processes contribute to a longer completion time. A secondary goal of the project was to identify methods to improve the time to completion and prevent excesses.

**Methods**

The study was performed at the VU University Medical Centre, an academic, urban, Level I trauma centre. There are approximately 35,000 ED visits per year of which 65% are patients who presented themselves without a referral. These patients are first seen by the emergency physicians. Referred patients are seen by the residents of various specialties under supervision of a specialist. One qualified emergency physician, four emergency medicine trainees and six non-trainee doctors worked at the ED during the study. The trainees and non-trainees were either supervised by an emergency physician or a senior surgeon. During four weeks in February 2010, data were collected from all patients presenting at the ED. A computer system called ‘Medical Office Data’ was used to extract data including: the moment of presentation/registration, referrer, discharge destination, and the main medical specialty involved in the care of the patient. Triage level and discharge time were obtained by paper forms filled out by nurses for all patients.

In addition, a researcher followed a selected group of patients to collect more detailed data about relevant timestamps in the ED process, which were not registered in the Medical Office programme. These data included the moment a doctor visited the patient, the moment blood or urine samples were taken, the moment laboratory results were received at the ED, and the moment a patient was picked up and brought back from an imaging study.

The Boston triage system (ESI) was used in the ED to indentify patients from ESI level 1 (highest acuteness) to ESI level 5 (lowest acuteness). The researcher followed patients with triage category ‘Emergency Severity Index’ 3 on weekdays from approximately 12:00 hours until 20:00 hours, because earlier data showed that this was the busiest time of the day, and that ESI 3 patients had longer completion times. This additional data collection lasted three weeks in February 2010 and provided a subgroup of 66 patients.

**Definitions**

Door-to-doctor time

We defined *door-to-doctor time* as the time that elapsed between registration and the first visit of a physician. Triage and the waiting time for a doctor are part of the *door-to-doctor time*.

Diagnostic tests

To get some insight into the role of diagnostic tests in the length of the ED stay, we divided the total time spent at the ED in three subprocesses.

- Prediagnostic tests: Time from arrival at the ED until the first request for a diagnostic test. For example: taking a blood sample and sending it to the laboratory, a request for an X-ray or CT scan, or a request for any other kind of diagnostic test.
- Diagnostic tests: Time between the request for the first diagnostic test until the results of the last diagnostic test are available. This also includes waiting times between different diagnostic tests.
- Time after diagnostic tests: Time from the last result of the diagnostic tests until discharge.

**Primary data analysis**

The patients were split into two groups: the patients who had a time to completion of shorter than four hours and the patients who spent longer than four hours at the ED. In addition, factors and processes that contributed to a longer time to completion were identified. For categorical factors, such as triage category and medical specialty, contingency tables were used. In every contingency table this division of patients is set against a categorical patient factor. For statistical analysis, the Pearson’s chi-square test was used. If the p value was smaller than 0.05, the null hypothesis was rejected. For subprocesses, such as *door-to-doctor time*, the time intervals were analysed. To calculate the time interval of a process, the data of the followed subgroup (n=66) were mainly used for these analyses. The time intervals of various processes were compared between patients who exceeded the four-hour target and the patients whose completion time was within four hours. The Mann-Whitney test was used for statistical analysis of these processes.

**Results**

**Time to completion (n=2510)**

In February 2010, 84% of the patients had a time to completion of less than four hours. Another 13% of the patients had a time to completion longer than four hours. Completion time data were not available for the remaining 3% of the patients. The average time to completion was 2:23 hours, the median was 2:01 hours. Figure 1 depicts the distribution of the time to completion. The largest group of patients had a completion time between one and two hours, while the longest measured time to completion exceeded 13 hours.
Arrival pattern (n=2444)
Most patients in the ED arrived between 09.00 and 22.00 hours (figure 2). No association was demonstrated between the arrival time of a patient and the four-hour target, p=0.49. No difference was found in exceeding the four-hour target between ED visits on week or weekend days as shown in figure 3, p=0.19.

Triage (n=2437)
Most patients (45%) were categorised as ESI 4, followed by ESI 3 (39%), as illustrated in figure 4. A large percentage of ESI 1, ESI 2, and ESI 3 patients did not achieve the four-hour target (22%, 19%, and 24%) compared with the patients categorised as ESI 4 or ESI 5 (5% and 1%). There was a dependency between the triage level and the
realisation of the four-hour target, \( p < 0.001 \). In absolute numbers, most patients who had a time to completion longer than four hours were ESI 3 patients.

**Door-to-doctor time \( (n=66) \)**
The average door-to-doctor time was 48 minutes. Half of the patients of the followed group had to wait less than 41 minutes for a doctor, as depicted in figure 5. The door-to-doctor time was not significantly different between patients who did or did not exceed the four-hour target, \( p = 0.37 \).

**Medical speciality \( (n=2144) \)**
Most patients were treated by the emergency physicians and 5% of this group had a time to completion longer than four hours. In absolute number and percentage, internal medicine had the most patients exceeding the four-hour target (37%), in percentage followed by neurology (29%) and surgery (28%). There is a dependency between the medical speciality and meeting the four-hour target, \( p < 0.001 \).

**Number of specialities involved \( (n=2444) \)**
If multiple specialists were involved in the care, patients were more likely to exceed the four-hour target than patients who were treated by only one speciality, \( p < 0.05 \). This is shown in figure 6.

**Diagnostic tests \( (n=66) \)**
The durations of the above-mentioned subprocesses were analysed for the subgroup, and are illustrated in figure 7. For 15 of the 66 followed patients, the division in subprocesses could not be made because no diagnostic tests were performed or data were incomplete.

From the three defined subprocesses, the duration of prediagnostic tests is the shortest, and the time after
diagnostic tests is the longest. The medians of the durations of the three subprocesses for all followed patients are 24, 62 and 78 minutes, respectively.

For prediagnostic tests, there is no significant difference in the duration for patients who do and do not exceed the target, \( p=0.23 \). For the other two subprocesses there is a significant difference in the durations for patients who do and do not exceed the target, \( p<0.001 \) and \( p=0.002 \), indicating that durations of these subprocesses influence the realization of the four-hour target.

Almost half of the patients at the ED (45%) underwent an X-ray, and 10% of the patients underwent a CT scan. The percentage of patients exceeding the four-hour target is almost the same for patients with and without an X-ray (11% and 16%). However, there is a dependency between undergoing a CT scan and exceeding the four-hour target, \( p<0.001 \).

**Discharge destination (n=2421)**

The largest group of patients is discharged home, with or without further treatment from their general practitioner or at an outpatient department (OPD), as depicted in figure 8. From all patients, 18% were admitted to the VUmc and 3% were transferred to another hospital for admission. In patients who were admitted to the VUmc or another hospital, a larger percentage exceeded the four-hour target than patients who were discharged home, \( p<0.001 \).

**Figure 8. Barplot of five main discharge destinations of ED patients with a completion time within four hours (dark) and ED patients with a completion time exceeding four hours (light); (n = 2421)**

**Figure 9. Realization of the four-hour target per age category (n = 2444)**

**DISCUSSION**

We demonstrated that 13% of the patients who presented at our ED had a time to completion longer than four hours. However, for patients categorised as ESI 3, this number was 24%. In addition, among the patients treated by internal medicine and neurology departments, 37% and 29% had a time to completion of more than four hours, respectively. Patients aged above 65 years, consultation of multiple specialities on the ED, ESI 3 category and usage of diagnostic tests such as a CT scan were also associated with a higher risk of exceeding the four-hour target. These patients are vulnerable to develop complications during a longer ED stay and therefore in need of effective and timely treatment strategy.

In the UK the four-hour target was introduced to ensure that patients do not wait too long in the ED from arrival to admission or discharge.\(^{14}\) In 2004, it was decided that 90% of the patients presenting to the ED should achieve this target. This target was raised to 98% in 2005 leading to a dramatic improvement in the congestion at the EDs. However, a spike in discharge or admission of patients during the last 20 minutes of the four hours was noticed, demonstrating that achieving the target had probably become a goal itself.\(^{2}\) A later study showed that this spike

**Age (n=2444)**

Compared with the rest, a significantly larger percentage of patients older than 65 years tended to stay in the ED for more than four hours (figure 9, \( p<0.001 \).
was still present and even larger than in 2004.9 After a heated debate the UK government decided to replace the four-hour target with a more balanced list of performance indicators with the aim of reducing the ED congestion and improving the acute care. Although some studies did not demonstrate beneficial effects on the quality of care with the strict enforcement of the target2 other studies have clearly shown that delays at the ED are associated with a worse prognosis and less patient satisfaction.7,8 Therefore, total time spent on the ED remains one of the indicators of quality of care in the UK.9 However, modern practice involves more investigations such as CT scans and more early treatments. As a result a few patients may benefit from a longer period of active treatment in the ED. There is a distinction to be made between unnecessary waiting and active treatment. Therefore, timelines will always remain an important element of any balanced approach to the quality of care. Frequently used measures in the UK to reduce the waiting times in the ED are additional senior doctor hours, creation of a four-hour monitor role, improved access to emergency beds or additional hours for nonclinical staff, junior doctors and nurses. No particular individual measure has been found to be the most important factor; rather it is the number of measures and the amount of effort which leads to improvement of the waiting time spent on the emergency department.6 Bucheli et al. concluded that additional physicians significantly reduced the length of stay of medical emergency department patients.2

In our study, although completion time of 84% seems satisfactory, most of the patients who stayed longer than four hours in the ED were old and vulnerable patients belonging to the ESI 3 category. In addition, there were patients who stayed much longer than the expected four hours. Consecutive consultations by different specialists, in patients with complex pathology, was one of the main reasons for these extreme delays. In our study it was evident that when a patient is treated by more than two specialties the chance of exceeding the four-hour target was high. The different specialties tended to work individually and not as a team. With the involvement of multiple specialties the coordination of care was lacking. Therefore, in our opinion different specialities should work as team and see these patients together rather than examining/treating these patients consecutively. We are in the process of introducing ‘assessment teams’ consisting of emergency physicians, internists, surgeons and a neurologist who will see a patient together with the aim of formulating a diagnostic/treatment plan. Internists or the emergency physicians will coordinate these assessment teams.

We also analysed a few subprocesses in our ED to discover which processes contributed most to a longer time to completion. One of the main findings of this subgroup analysis was that the elapsed time between receiving all diagnostic results and admission/discharge had the biggest influence on the time to completion. In our opinion this is probably due to the delay in decision-making, although this was not tested in our study.

In our opinion, one of the possible causes for this delay in decision-making is that junior doctors treat most of the patients and need time to consult the case with their supervisors. Furthermore, the junior doctor sometimes has to wait before he can proceed because the supervisor is busy with multiple patients. In addition, especially during the night, the junior doctors tend to collect patients before phoning the specialist for advice, so that the specialist would not be disturbed too many times during sleep. Another reason for delay is that it takes time before test results are available, or because the doctor was not aware of the fact that the diagnostic tests have already been performed.

For patients admitted to the hospital, the time after diagnostic tests is even longer than for patients who are discharged home. This is probably caused by the limited availability of hospital beds which leads to a time-consuming search for a bed or transfers to other hospitals. Creating an acute medical unit (AMU), observation beds or more inpatient beds may solve this problem.22,23 Not all AMUs will achieve the same results but numerous studies have shown beneficial effects on length of stay, mortality, readmission rates and lower costs per admission when an AMU is well run.24 At present there is no AMU at the VUmc but we are planning to open an acute medical unit within a few months.

After the results were known, several measures were introduced in our department to shorten the length of stay on the ED for patients. The measures mainly focussed on improving supervision and coordination. We are in the process of increasing the number of emergency physicians to cover all the shifts 24/7. The working hours of senior doctors in the internal medicine and surgery department on the emergency room have been adjusted to cover the busiest moments at the ED (12.00 hours to 22.00 hours). A study in the UK showed that presence of a consultant might have positive effects on the patient length of stay and decision-making.25 For this reason, a coordinating physician has been appointed 24/7 and regular time out moments have been created five times a day. During these time outs the head nurse and coordinating physician analyse if queuing or any other logistical problem occurs and if necessary measures are taken to solve these problems as soon as possible. Furthermore, preferential service levels have been agreed with the radiology and other departments. Cases with time to completion of more than four hours are discussed on a regular basis and

Vegting et al. Completion times in an academic emergency department.
structural problems are solved when possible. The number of emergency physicians will be extended in the coming months with the aim of having an emergency physician in the ED during all the shifts. Another strategy to improve health outcomes of acute patients is to start treatment as soon as possible in the ED, for example: administration of antibiotics.26 Steps have already been taken to implement these measures in our ED. We are planning to investigate the results of all these measures in a following study.

**STUDY LIMITATIONS**

The period used to collect data covered only four weeks. This means that seasonal influences which can alter the patient population in the ED have not been accounted for. Furthermore, the subgroup analysis is based on a small group of 66 patients. The reason for this relatively small group is that it is time consuming to record all steps in the processes on the ED due to lack of an electronic tracking system. This is a single-centre study, which can influence results due to regional practice variation or because of the chance that a specific doctor is absent during the study period. However, we do not think this was a problem since this is a large hospital with a wide variety of specialities and many specialists. No specific speciality was under-represented during the study.

**CONCLUSION**

In this cross-sectional study we demonstrated that a significant percentage of vulnerable and ill patients tend to exceed the four hours spent in our ED. The lack of coordination of care in vulnerable patients contributed most to this stagnation. Improving the coordination of care will in our opinion lead to significant reduction in ED queuing.
Case Report

A 31-year-old woman of Turkish origin was referred because of hypercalcaemia. She had experienced myalgia and bone pain for years. She further experienced progressive fatigue, poor memory and general muscle weakness. Six months before presentation, she had been diagnosed with vitamin D deficiency, for which supplementation was started. Her symptoms did not improve. Medical consultation during a holiday in Turkey yielded hypercalcaemia.

At physical examination she was obese and walked with difficulty. There were no signs of arthritis and motion of the hips was not limited. Laboratory evaluation revealed an albumin-corrected calcium of 3.07 mmol/l (URL 2.65), parathyroid hormone (PTH) 100 pmol/l (URL 6.5), 25 OH vitamin D3 18 nmol/l (LRL 35), 1,25 (OH)2-vitamin D3 429 pmol/l (URL 150) and creatinine 50 μmol/l (N 50-90).

The alphacalcidol was stopped at presentation because of hypercalcaemia.

The source for PTH hypersecretion was identified as a 3 cm tumour of the left lower parathyroid by tetraphosmin scintigraphy. A pelvic X-ray (figure 1) showed a large lytic lesion of the right acetabulum extending into the ilium and ischium at high risk of fracture; more lytic lesions were present in the right and left ilium. Trabeculae were clearly visible in the neck of both femurs. The bone scintigraphy (figure 2) showed multiple focal lesions and accumulation at the skull, costochondral joints and the cortex of the long bones.

What is your diagnosis?

See page 403 for the answer to this photo quiz.
A 37-year-old Philippine sailor with an unremarkable medical history visited the outpatient clinic of the Havenziekenhuis in Rotterdam. The patient initially noticed nodules in his face which spread over his body in a period of two weeks. He had also noticed a larger skin lesion with decreased sensitivity and paresthesia on his right elbow. In the past few months he had been travelling to India and South Africa.

Clinical examination showed a generalised papulo-nodular eruption (figure 1a). The diameter of the lesions varied between 0.5 and 5.0 cm. On the right elbow and lower arm there was a larger erythematous plaque-like skin lesion with numbness and central hypopigmentation (figure 1b).

Laboratory tests revealed signs of intravascular haemolysis. Direct antiglobulin test and test for enzymatic erythrocyte disorders were negative. Skin biopsies showed a granulomatous inflammatory process, with a clear zone near the epidermis (figure 2a). Additional Ziehl-Neelsen and Wade-Fite staining (figure 2b) revealed the presence of numerous acid-fast bacilli.

WHAT IS YOUR DIAGNOSIS?

See page 404 for the answer to this photo quiz.
Case Report

A 71-year-old woman was referred to the neurology department with unilateral sensibility loss of the face, which had developed over several days. Her medical history included arteritis temporalis and multiple myeloma, with an IgA-Lambda M-protein level of 49 g/l at onset, one year before presentation. The patient was treated with melphalan, thalidomide and prednisolone, and she was in complete remission five months before presentation. Physical examination revealed a subjective sensibility loss of the face, without other abnormalities. Laboratory investigations showed no abnormalities in kidney function, liver enzymes, electrolytes or inflammatory markers. No M-protein was detected. Magnetic resonance imaging of the brain and spine revealed a mass close to the left nervus trigeminus, suggestive for a schwannoma or a meningeoma. However, the patient showed a rapid deterioration of her neurological condition, with the onset of dysphagia and a paresis of the right foot. Because of this symptomatology, analysis of the cerebrospinal fluid (CSF) was performed (figure 1).

Photo Quiz

Facial numbness as a symptom of a systemic disease

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Figure 1. Cerebrospinal fluid showing abnormal cells

What is your diagnosis?

See page 405 for the answer to this photo quiz.
A 44-year-old man presented to the emergency department with a four-day history of dyspnoea, productive cough and haemoptysis. His past medical history was significant for asthma, smoking, and chronic alcohol abuse. Two weeks prior to presentation he had an episode of protracted vomiting, followed by a fall, head contusion and subsequent transient loss of consciousness.

The patient appeared neglected, with moderate respiratory distress. He was conscious and afebrile, with a respiratory rate of 32 breaths/min, a pulse rate of 120 beats/min, and blood pressure of 58/44 mmHg. Pulse oximetry showed an oxygen saturation of 96% at room air. Chest examination revealed reduced air entrance to both lungs, with rhonchi heard at the right lung base. Significant laboratory findings were a white blood cell count of 19,000 cells/mcL with 93% neutrophils, haemoglobin level 11.6 g/dl, platelet count 217 platelets/μl, serum creatinine level 335 μmol/l, sodium 131 mmol/l, albumin 28 g/l and C-reactive protein 60 mg/dl (normal values 0 to 1). Liver-associated enzyme levels were normal. Blood gases showed pH of 7.26 with PCO2 49 mmHg and HCO3 21 mmol/l.

Antero-posterior chest X-ray (figure 1) and chest computed tomography (figure 2) showed diffuse bilateral infiltrates in both lung bases with a 6 cm cavitation in the upper segment of the right lower lobe.

WHAT IS YOUR DIAGNOSIS?

See page 406 for the answer to this photo quiz.
DIAGNOSIS

The combination of hyperparathyroidism and lytic bone lesions raised suspicion of a brown tumour as a consequence of hyperparathyroidism caused by parathyroid adenoma. The initial vitamin D deficiency might have aggravated the hyperparathyroidism. The parathyroid adenoma was surgically removed, resulting in normal PTH levels. A biopsy of the acetabulum lesion confirmed the diagnosis of a brown tumour. In the course of months remineralisation of the bone lesions occurred. The primary treatment of brown tumours consists of resolving the hyperparathyroidism. Surgical treatment of the bone lesions is only indicated in cases of (high risk for) fracturing. Although clinical features can be highly suggestive for brown tumours, histological evidence is indispensable to rule out malignancy. Histologically, brown tumours are characterised by increased numbers of osteoclasts, cyst formation, signs of increased bone turnover and fibrosis. The chaotic bone matrix does often result in focal necrosis and microfractures. Haemosiderin deposits because of bleeding give these tumours their characteristic brown colour.

Brown tumours are a late feature of osteitis fibrosa cystica. Osteitis fibrosa cystica develops as a consequence of a disturbed balance between bone formation and degradation due to exposure to high PTH levels. It is radiologically characterised by multiple lytic bone lesions, subperiostal resorption of the distal phalanges and clavicles, absence of the lamina dura of the teeth, focal demineralisation of the skull and low bone density. On bone scintigraphy focal areas of accumulation can be accompanied by features of metabolic bone disease, such as excessive activity of the skull, the costochondral joints (rosary sign) and the cortex of the long bones (tramline phenomenon).

REFERENCES

**DIAGNOSIS**

A diagnosis of borderline lepromatous leprosy, also known as a type of multibacillary leprosy, was made. The diagnosis was confirmed by a leprosy-specific PCR, using Mycobacterium leprae specific repetitive element (RLEP). An ELISA for specific M. leprae anti-phenolic glycolipid-1 (anti-PGL-1) was also positive.

**DISCUSSION**

Leprosy, caused by infection with M. leprae, is an ancient disease with a broad clinical spectrum which involves skin and peripheral nerves. The specific host cellular immune response is responsible for its clinical disease manifestations. As a consequence of an impaired cellular immunity in the lepromatous type of leprosy, the leprosy bacteria can proliferate and infiltrate the tissues without restraint. The plaque-like lesion near the elbow is considered an immune area with signs of localised T-cell-mediated immune reaction, also known as an upgrade in the lepromatous spectrum towards the tuberculoid pole.

Leprosy may also present with systemic features such as haemolytic anaemia, probably as a reaction to extensive infiltration with M. leprae. Haemolytic anaemia is a well-known complication of treatment with dapsone due to its oxidative stress effect on erythrocytes. In contrast, our patient had not received prior treatment with dapsone. Additional tests revealed no other clue for the haemolysis than systemic reaction to massive infiltration with M. leprae. When multidrug treatment (MDT) for leprosy was initiated, which includes treatment with dapsone, frequent laboratory tests were performed to monitor progression of haemolysis. Fortunately, haemolysis did not worsen by treatment with dapsone.

Since the introduction of MDT for leprosy, the worldwide prevalence has decreased considerably. Due to unfamiliarity with the disease in non-endemic industrialised countries, the diagnosis of leprosy is often not considered which may result in a significant delay in starting the appropriate treatment aiming at preventing permanent nerve damage and disability. In the Netherlands it will take on average six years from the start of the first disease symptoms to administration of MDT. Early case detection and MDT are of paramount importance to improve the clinical outcome of leprosy and are also key elements in the elimination of leprosy as a public health problem.

**REFERENCES**

Analysis of the CSF showed atypical plasma cells suggestive for the diagnosis multiple myeloma (MM) with involvement of the central nervous system (CNS). Additional flow cytometric analysis of the CSF revealed a monoclonal plasma cell population with a strong expression of CD38 and cytoplasmic IgA-Lambda (figure 2), which confirmed the diagnosis mentioned above.

MM is characterised by the presence of monoclonal proliferating plasma cells, usually restricted to the bone marrow. The current treatment and prognosis of this disease have improved due to the introduction of a novel generation of drugs. These drugs are combined with more traditional chemotherapy and in younger patients possibly autologous stem cell transplantation.1 CNS involvement of MM is a rare complication with an estimated incidence of approximately 1%.2 It is defined by the presence of monoclonal plasma cells in the CSF. Evidence of monoclonality is mandatory, as plasma cells can be seen in several infectious and non-infectious conditions. The exact aetiology remains unknown. Several hypotheses are 1) direct continuous spread of osteolytic skull lesions; 2) haematogenous spread of plasma cells seen in plasma cell leukemia, or the spread of lymphoid cells, progenitors of plasma cells; and 3) continuous growth of plasma cells in the CNS during the course and treatment of MM, while the drugs used in MM cannot pass the blood-brain barrier.3 The clinical presentation covers a diffuse array of neurological symptoms and signs. Treatment options include combinations of systemic chemotherapy, intrathecal chemotherapy and cranial irradiation. Autologous stem cell transplantation can be considered when the patient is in a good clinical condition. Despite treatment, CNS involvement of MM has a poor prognosis with a median survival of two months.'4

Our patient started intrathecal chemotherapy (cytarabin); however, the neurological symptoms worsened rapidly and she died three weeks after the diagnosis was made.

REFERENCES

Figure 2. Immuno-flow cytometric analysis of CSF showing strong expression of CD38 and cytoplasmic expression of Ig light chains Lambda (CyLambda) (left figure) and IgA (CyIgA) (right figure) by the monoclonal plasma cells
Cavitary pneumonia and septic shock caused by *Pseudomonas aeruginosa*.

Anteroposterior chest X-ray and chest computed tomography at presentation showed diffuse alveolar infiltrates with a large cavitary lesion in the right lower lobe. In view of the uncertainty of the diagnosis and the patient’s clinical condition, intravenous ceftriaxone, azithromycin and metronidazole were administered. Soon after, intubation and mechanical ventilation were instituted due to respiratory failure and shock and the patient was admitted to the intensive care unit. Despite intensive antibiotic and supportive treatment, multi-organ failure supervened and the patient died within two days of admission. *Pseudomonas aeruginosa* was recovered from blood and sputum cultures.

While *P. aeruginosa* is a common aetiological agent of nosocomial pneumonia, community acquired pneumonia (CAP) caused by *P. aeruginosa* is uncommon. In a recent prospective study of 5130 patients, the overall incidence of CAP caused by *P. aeruginosa* was only 0.4% with an 18% mortality rate. The proportion of *P. aeruginosa* is higher among patients presenting with rapidly progressive pneumonia which necessitates intensive care treatment. Most reports of CAP caused by *P. aeruginosa* are in patients with pulmonary comorbidity, immune suppression, following hospitalisation or within 30 days of antimicrobial therapy.

*P. aeruginosa* CAP can be rapidly progressive, presenting as necrotising pneumonia with cavitary lesions on chest radiography with predilection for lower lobes. The high mortality rate is partly due to inadequate empirical antimicrobial treatment.

Our patient had chronic lung disease and chronic alcohol abuse as predisposing risk factors and the possibility of *P. aeruginosa* CAP could be suggested by the severity of his disease and its rapid progression. When a patient presents with severe rapidly progressive necrotising pneumonia and relevant risk factors, a high index of suspicion for *P. aeruginosa* CAP is required and empirical anti-pseudomonas antimicrobial treatment should be considered.

**REFERENCES**