Procalcitonin in bacterial infections – hype, hope, more or less?

Mirjam Christ-Crain, Beat Müller
Department of Internal Medicine, University Hospital, Basel, Switzerland

Summary

An ideal marker for bacterial infections should allow an early diagnosis, inform about the course and prognosis of the disease and facilitate therapeutic decisions. Procalcitonin (ProCT) covers these features better as compared to other, more commonly used biomarkers, and thus, the current hype on ProCT has a solid scientific basis. A superior diagnostic accuracy of ProCT has been shown for a variety of infections, e.g., respiratory tract infections, meningitis, acute infectious endocarditis and pancreatitis. Importantly, a ProCT-based therapeutic strategy can safely and markedly reduce antibiotic usage in lower respiratory tract infections, the major cause of sepsis. Being a hormokine mediator, immunoneutralisation of ProCT might offer new hope for more effective treatment options in sepsis. It is now evidence-based that ProCT provides more information and, thereby, questions the currently used “gold standards” for the diagnosis of clinically relevant bacterial infections. Yet, ProCT is less than a perfect marker. ProCT can be increased in non-infectious conditions, and may remain low in infections. The diagnosis of bacterial infections will continue to require a critical clinical awareness, careful patient history, dedicated physical examination, and appropriate cultures. This review aims to help the clinician to understand the physiopathological basis, to appreciate strengths and weaknesses of this biomarker, and thereby to promote a rational implementation of ProCT in a routine setting.

Key words: infection; procalcitonin; diagnosis; sepsis

What is procalcitonin?

Procalcitonin (ProCT) is a precursor peptide from the hormone calcitonin (CT) [1] (figure 1). After translation from CT-messenger RNA (mRNA), ProCT is cleaved enzymatically into smaller peptides, finally to yield the thirty-two amino acid mature CT [2]. Most CT precursor peptides, including ProCT, are found in the serum of normal persons.

Mature calcitonin (CT), named after its mild and transient hypocalcaemic effect, was originally thought to be a hormone exclusively of thyroidal C-cell origin and to play an important role in skeletal homeostasis [3, 4]. However, provided that thyroid hormone is replaced, thyroidectomy in humans has no important pathologic consequences: calcium homeostasis remains intact and bone density is not decreased [5, 6]. Possibly, different CT peptides (e.g., CT, CT gene related peptide [CGRP]) had once an evolutionary role in becoming vestigial in the context of establishing, protecting and regulating the skeletal mass [7]. However, the presence of the parathyroid gland and other evolutionary changes occurring in tetrapods suggest that the function of the mature CT hormone in humans is no longer essential [8].

Conversely, in microbial infections and in various forms of inflammation, circulating levels of several calcitonin precursors, including ProCT but not mature CT, increase up to several thousand-fold. This increase and especially the course correlates with the severity of the condition and with mortality [9–12].
ProCT – the molecular basis for the increase in inflammation and infection

In the traditional endocrine view, mature CT is produced mostly in neuro-endocrine C-cells of the thyroid. In the absence of infection, the extra-thyroidal transcription of the CALC-I gene is suppressed and is restricted to a selective expression in neuro-endocrine cells found mainly in the thyroid and lung. In these neuroendocrine cells, the mature hormone is processed and stored in secretory granules [4, 13].

Interestingly, a microbial infection induces an ubiquitous increase of CALC-I gene-expression and a constitutive release of ProCT from all parenchymal tissues and differentiated cell types throughout the body [14] (figure 2). Thus, under

Figure 1
Schematic illustration of human procalcitonin. Procalcitonin and its constituent peptides, which are found in the free form in normal human serum. Initially, procalcitonin consisting of 116 amino acids is secreted. Due to rapid cleavage by dipeptidases, 114 amino acid long procalcitonin is found in the circulation. Additional cleaving leads to circulating aminoprocalcitonin, immature calcitonin and calcitonin carboxypeptide-I (CCP-I), previously known as katacalcin. In sepsis, these peptides are variably increased, often to huge levels due to ubiquitous expression and secretion. However, in this condition, serum levels of mature calcitonin, which is only produced by thyroidal c-cells, remain normal or are only slightly increased.

Figure 2
Schematic diagram of CALC I expression in adipocytes and thyroidal C cells. In the classical neuroendocrine paradigm, the expression of CT mRNA is restricted to neuroendocrine cells, mainly C cells of the thyroid. Initially, the 116-amino acid prohormone ProCT is synthesised and subsequently processed to the considerably smaller mature CT. In sepsis and inflammation, both proinflammatory mediators and bacterial toxins induce CT mRNA, which can be attenuated by interferon γ. In contrast to thyroidal cells, parenchymal cells (e.g., liver, kidney, adipocytes and muscle) lack secretory granules, and hence, unprocessed ProCT is released in a non-regulated, constitutive manner. Adapted from [13].
In septic circumstances, the entire body could be viewed as being an endocrine gland. Indeed, the transcriptional expression of CT-mRNA is more uniformly up-regulated in sepsis than are the mRNAs of the classical cytokines (e.g., tumour necrosis factor (TNF)-α and interleukin (IL)-6). There is a relatively low and only transient expression of ProCT in the white blood cells [14–16]. Importantly, no CT gene expression is found if these cells are harvested from septic patients with markedly elevated serum ProCT levels. In whole blood, LPS-stimulation is unable to induce any detectable ProCT production by leukocytes. Moreover, high serum ProCT levels in septic patients after near-complete eradication of the leukocyte population by chemotherapy suggest that these cells are not a major source of ProCT. Parenchymal cells (including liver, lung, kidney, adipocytes and muscle) provide the largest tissue mass and principal source of circulating ProCT in sepsis [13]. The greater ProCT mRNA induction and ProCT peptide release from parenchymal cells in comparison to circulating cells, appears to indicate a tissue based, rather than a leukocyte based mechanism of host defense. Thus, CALC-gene products are a prototype of hormokine mediators and can follow either a classical hormonal expression in neuro-endocrine cells or, alternatively, a cytokine-like ubiquitous expression pathway in various cell types [14]. The inflammatory release of hormokines can be induced either directly via microbial toxins (e.g., endotoxin) or indirectly via a humoral or cell-mediated host response (e.g., IL-1β, TNF-α, IL-6). The induction can be attenuated by cytokines also released during a viral infection (e.g., interferon-γ). In sepsis, the predominance of ProCT as opposed to mature CT is indicative of a constitutive pathway within cells lacking secretion granules and, hence, a bypassing of much of the enzymatic processing [13]. Consequently, as is the case for most cytokines, there is very little intracellular storage of ProCT in sepsis [14].

How to measure ProCT levels

For the diagnosis of infections, the diagnostic accuracy of ProCT and its optimum cut-offs are completely dependent on the use of a sensitive assay in a predefined clinical setting (figure 3). Ideally, an ultra-sensitive assay should reliably measure circulating concentrations of ProCT in all healthy individuals. Such assays are currently available for research purposes (PCT sensitive® and N-ProCTKLB®) and should be made widely available for the clinician in the near future. A rapid assay assures that results can be timely incorporated into clinical decision making.

We recently evaluated a newly developed ProCT assay for the guidance of antimicrobial therapy in lower respiratory tract infections [17]. This commercially available assay takes advantage of a time-resolved amplified cryptate emission (TRACE) technology (Kryptor® PCT, Brahms, Hennigsdorf, Germany). It is based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-katacalcin antibody, which bind to the calcitonin and katacalcin sequence of calcitonin precursor molecules. The assay has a functional assay sensitivity of 0.06 μg/L, i.e., 3- to 10-fold above
Procalcitonin in bacterial infections – hype, hope, more or less?

ProCT in bacterial infections

Procalcitonin (ProCT) is a biomarker that can be measured in serum and is useful in the diagnosis of bacterial infections, especially in sepsis. It is a sensitive indicator of bacterial infection, with levels rising before other inflammatory markers. However, ProCT levels can also be elevated in viral infections, making it less specific.

Limitations of ProCT

The sensitivity of ProCT in sepsis is limited. Levels can be within the normal range, even in severe sepsis, which can lead to diagnostic uncertainty. It is important to consider other markers and clinical findings when interpreting ProCT levels.

Antimicrobial therapy

ProCT can be used as a tool to guide antimicrobial therapy. In the “ProResp” study, patients with febrile respiratory tract infections were randomized to receive standard treatment or ProCT-guided therapy. The ProCT-guided group had a lower rate of antibiotic treatment compared to the standard group.

Conclusion

ProCT is a promising tool for the diagnosis and management of bacterial infections. However, its limitations and potential for false positives must be considered in clinical practice.
strongly encouraged >0.5 μg/L. Baseline characteristics were similar in the standard group as compared to the ProCT group. The clinical and laboratory outcome after a mean of 13.0 ± 4.4 days was similar in both groups. In the ProCT group the percentage of patients with LRTI, who received antibiotic therapy was reduced by 46.6%, as compared to the standard group (p <0.001). Antibiotic use could be significantly reduced in all diagnostic subgroups, but most striking in acute bronchitis and acute exacerbations of chronic obstructive pulmonary disease.

Pneumonia is defined as inflammation of the pulmonary parenchyma, which is often caused by a bacterial agent and mirrored in markedly elevated ProCT levels [12, 35]. Antimicrobial therapy must be promptly initiated, because a delay of >8 h in treatment is associated with increased mortality [37]. Unfortunately, bacteria are usually identified in less than 50% of cases and a positive viral serology does not rule out complicating bacterial infection. In the clinical context of CAP, the primary value of ProCT is not the reduction of antibiotic prescription, but to facilitate the differential diagnosis of new or progressing infiltrates. Accordingly, ProCT-guidance could markedly lower the number of antibiotic courses in patients with infiltrates on chest x-ray unrelated to pneumonia. Recently, we could show in the “ProCAP”-study including more than 200 patients cut-off is currently being investigated in the “ProCOLD”-study including more than 200 patients with acute exacerbations of COLD. Upper respiratory tract infections are commonly seen in general practice and also often unnecessarily treated with antibiotics. Whether ProCT guidance can reduce antibiotic use in upper and lower respiratory tract infections, in general practice, is also currently being investigated (“PARTT”-study).

ProCT – a marker for other infectious diseases?

The diagnosis of bacterial infections of extrapulmonary sites remains a challenge for clinicians. The general consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a specific marker for bacterial infection would be helpful. Usual markers such as fever, leucocytosis with increased rate of polymorphonuclear cells (or leucopenia), and elevation of CRP, respectively, are sometimes helpful. A positive culture result has a relative high specificity, but even this is not a gold standard, because it lacks sensitivity and the results are only available after 2 to 3 days. Despite this fact, many researchers use the positive blood culture plus clinical signs of infection as a positive gold standard, and patients without any clinical evidence plus a negative blood culture as the negative gold standard. This forces all patients to be omitted who cannot be classified unambiguously from the analysis [77]. Such an analysis probably circumvents the problem of misclassification bias, at the price of introducing a new bias.

The results of a recent meta-analysis showed that ProCT is a more accurate marker for systemic bacterial infections independent of the source as compared to CRP levels, both when differentiating bacterial infections from non-infective causes of inflammation and when differentiating bacterial infections from viral infections [42]. Thereby, pooled sensitivity for ProCT was 88% (95%CI 80–93%), compared with 75% (95%CI 62–84%) for CRP levels. Pooled specificity for ProCT was also significantly better as compared to CRP in differentiating bacterial infections versus viral infections. Pooled sensitivity for ProCT was 92% (95%CI 86–95%) and for CRP 86% (95%CI 65–95%). Pooled specificities were comparable (73%, 95%CI 42–91%) for ProCT and 70%, 95%CI 19–96%, for CRP.

This superior diagnostic performance of ProCT has been shown for a variety of infections [23, 43], eg for meningitis [11, 44], infectious endocarditis [45, 46], pancreatitis [46–49], and others [36].

Serum ProCT is more accurate than the currently available markers for differentiating between viral and bacterial meningitis in both chil-
dren and adults [50, 51]. Conversely, there is a large overlap of usually determined parameters like glucose, proteins and cells of the cerebrospinal fluid and, to a lesser extent, CRP concentrations.

The variability in the clinical presentation of infectious endocarditis makes the diagnosis a clinical challenge. The use of current imaging techniques in the diagnosis of infectious endocarditis is also suboptimal. For example, echocardiography detected infective endocarditis in only 43 of 300 consecutive patients [52]. A simple blood test to predict the presence or absence of infectious endocarditis in suspected cases would be highly desirable. In acute infectious endocarditis, ProCT levels are significantly higher as compared to patients with other final diagnoses [53]. In a recent study, ProCT was the only significant independent predictor of acute infectious endocarditis on admission in a multivariate analysis, in contrast to other parameters like CRP. The diagnostic accuracy was comparable to that of B-type natriuretic peptide for the emergency diagnosis of heart failure [45, 54]. Using a cut-off of 2.3 µg/L, ProCT for the diagnosis of acute infectious endocarditis had a sensitivity of 81%, a specificity of 85%, a positive predictive value of 72% and a negative predictive value of 92%. A word of caution must be added. In some patients, especially with sub-acute endocarditis, ProCT levels may remain very low [55, 56]. Thus, beyond doubt, the diagnosis of infectious endocarditis, as all other infectious diagnoses, will continue to require a critical clinical awareness, careful patient history, dedicated physical examination and blood cultures in all patients. The use of ProCT, albeit not being a perfect marker, might still help to significantly improve the resource utilisation of diagnostic imaging.

Patients with oedematous or toxic pancreatitis have low concentrations of ProCT whereas patients with infectious pancreatitis have very high ProCT concentrations [46]. This is especially useful for the monitoring of these patients in whom secondary infection of the initial pancreatic focus might necessitate surgical intervention. ProCT levels in pancreatitis may reflect the derangement in gut barrier function (rather than the extent of systemic inflammation) and may hence predict those patients in whom the translocation of bacteria and fungi into dead pancreas with subsequent infected necrosis is more likely [48, 57].

Data on the clinical use of ProCT in diverticulitis or other gastro-intestinal infections are lacking.

In patients with localised infections, ProCT is usually lower as compared to patients with generalised infections and positive blood cultures, as expected. In strictly localised infections there is a pronounced increase in ProCT levels only if the infection involves surrounding tissues or becomes systemic. In a closed focus, ProCT concentrations are only moderately high, as in some cases of infectious arthritis in adults [58].

ProCT in urinary tract infections is useful in the absence of well-identified severity markers [59]. In a paediatric study, ProCT unlike TNF, IL-6, IL-8 or CRP was correlated with the severity of renal scars caused by the infection itself, as assessed by scintigraphy [60].

Malaria is the main infectious condition, other than bacterial infections, in which ProCT concentration is high [61]. Even in simple bouts of malaria without neurologic complications, the levels reached are frequently high. The reason for the increased ProCT levels in malaria patients is probably the elevated TNFα level [62]. It is known that large quantities of ProCT are produced after perfusion of TNFα in humans [63].

**ProCT – More than “just” a marker in bacterial infections?**

Importantly, ProCT, likely together with other calcitonin precursors, contribute to the deleterious effects of systemic infection. The administration of ProCT to septic hamsters with peritonitis doubled their death rate, reaching levels exceeding 90%. Furthermore, treatment with ProCT-reactive antiserum increased the survival of septic hamsters [64–66]. In addition, a one-hour intravenous immunoneutralisation using an antiserum, reacting specifically with porcine ProCT, improved the physiologic and metabolic parameters of septic pigs, and greatly increased their short-term survival (from 0% to 80%) [67]. Furthermore, recent experiments have demonstrated that such immunoneutralisation is effective even when administered after the animals are moribund [68].

Thus, these observations indicate that ProCT is also a potentially harmful mediator involved in the septic response. It was shown, that ProCT acts as a modulator of the inflammatory/immunologic host reaction [69]. Furthermore, ionised hypocalcaemia is more pronounced with increasing severity of infection, and occurs in parallel with the marked increase of ProCT [70]. In contrast, as mentioned above, serum levels of mature CT are normal or only minimally elevated in sepsis [10, 11, 70].

Several characteristics of ProCT favour this hormone molecule as a therapeutic target in sepsis. In contrast to the transiently increased classical cytokines, for which immunoneutralisation trials in humans have been disappointing, the massive increase of circulating ProCT persists for several days [71]. Furthermore, ProCT is very frequently increased in overt sepsis, its onset is early (within 3 hr), and the diagnostic accuracy of the measurement should greatly improve patient selection for any study of the therapeutic efficacy of ProCT immunoneutralisation and antibiotic therapy in humans.
ProCT can be a bad marker for infections!

New tests are developed at a fast rate and the technology of existing tests is continuously being improved. For every diagnostic marker, exaggerated and biased results from poorly designed and reported diagnostic studies can trigger their premature dissemination and lead physicians into making incorrect, potentially dangerous treatment decisions [72]. This is also a major risk for a new and promising marker like procalcitonin.

For example, it has been suggested that a ProCT <0.4 µg/L accurately predicts the absence of bacteraemia in adult patients with acute fever, and antibiotic treatment can be safely withheld until additional diagnostic information becomes available [73]. In our opinion, such data have to be interpreted very cautiously and over-enthusiastic conclusions and the resulting hype are potentially dangerous. Clearly, low levels of ProCT <0.4 µg/L can be seen in subacute infectious endocarditis with bacteraemia. Clinically apparent infections are a sequel of complex and variable interactions between host immune response, microbes and their toxins. Obviously, the resulting clinical syndrome is far too complex to be reduced to a single cut-off of any specific surrogate marker.

The optimal cut-off ranges of ProCT are variable and dependent on:
- the clinical setting (eg primary care, emergency room, intensive care unit, post-operative or trauma patients)
- the site and extent of the infection (eg RTI, endocarditis, meningitis, others)
- co-morbidities (eg impaired pulmonary reserve, immunosuppression)
- the clinical implications drawn (eg diagnosis, prognosis, antibiotic stewardship)

For the majority of infections optimal cut-off ranges remain still to be determined in observational studies and validated in intervention studies.

<table>
<thead>
<tr>
<th>Common causes of false-negative and false-positive results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>false-positive (ie, falsely high levels in the absence of a bacterial infection):</td>
</tr>
<tr>
<td>newborns (physiologically) during first days of life [78]</td>
</tr>
<tr>
<td>acute respiratory distress syndrome [79, 80]</td>
</tr>
<tr>
<td>acute attacks of plasmodium falciparum malaria [61]</td>
</tr>
<tr>
<td>systemic fungal infections (eg candidiasis, aspergillosis) [81]</td>
</tr>
<tr>
<td>severe mechanical trauma [82]</td>
</tr>
<tr>
<td>following surgical trauma [83]</td>
</tr>
<tr>
<td>administration of monoclonal or polyclonal anti-thymocyte globulin in the treatment of acute rejection after transplantation [84]</td>
</tr>
<tr>
<td>chemical pneumonitis [85]</td>
</tr>
<tr>
<td>severe burns and heat strokes [86, 87]</td>
</tr>
<tr>
<td>patients with medullary thyroid cancer, small cell cancer of the lung, carcinoid, tumours with paraneoplastic hormone production [88]</td>
</tr>
<tr>
<td>inflammation associated with “cytokine storms”, eg ILβ, in familial Mediterranean fever, therapeutic infusions of TNFα in melanoma [13, 16]</td>
</tr>
<tr>
<td>false-negative (ie, falsely low levels in the presence of a bacterial infection):</td>
</tr>
<tr>
<td>early course of infections [17]</td>
</tr>
<tr>
<td>localised infections [58]</td>
</tr>
<tr>
<td>subacute endocarditis [55, 56]</td>
</tr>
</tbody>
</table>

ProCT is not a very early marker of infection
Follow-up and re-evaluation of ProCT in clinical suspicion of infection is pivotal

A single ProCT value on admission is not a very good prognostic marker
Although higher in patients who survive as compared to non-survivors, ProCT is rather a diagnostic than a prognostic marker. In contrast, the course of ProCT has prognostic implications [39, 89]

Costs
ProCT is more expensive as compared to other biomarkers (eg CRP), for which, however, no intervention studies exist.

Different assays available with very different test performances
The diagnostic accuracy of ProCT is completely dependent on using a sensitive assay in an appropriate, defined clinical setting [34]
Ultra-sensitive assays to determine subtle elevations of ProCT are not yet widely available.
ever, it cannot be overemphasised that the diagnostic accuracy of ProCT and its optimal cut-offs are completely dependent on using a sensitive assay in an appropriate clinical setting with a pre-test probability for the presence of a specific infection. ProCT is never a substitute for a careful history and physical examination. A clinician should withstand the temptation to rely solely on the result of a laboratory test rather than to interpret a demanding clinical examination.

As is the case for all diagnostic tests, a serum ProCT level must always be evaluated and re-evaluated during follow-up, respectively, with proper regard to the clinical context. The potential limitations and weaknesses of ProCT are summarised in Table 1. Importantly, circulating ProCT levels can be increased in non-infectious conditions, and may remain relatively low even in sepsis induced by bacterial infections [34, 36, 74]. In cases of falsely high ProCT levels, in the absence of an infection (typically seen after severe trauma or surgery), ProCT levels are usually moderately elevated between 1 and 10 μg/L, but decline rapidly to values below 1 μg/L within 48 hours. Persistently high ProCT levels in these patients make again the presence of a complicating bacterial infection likely. Conversely, falsely low ProCT levels (typically seen during the early course or localised state of an infection) often show a gradual increase during follow-up measurements after 6 to 24 hours and thereby point to an underlying bacterial disease. This again, stresses the importance of follow-up measurements. Further studies for the comparison of ProCT with other emerging and promising diagnostic markers of bacterial infections (eg soluble triggering receptor expressed on myeloid cells [sTREM]) are strongly encouraged [75]. It is likely that other biomarkers can complement the diagnostic and prognostic power of ProCT.

Conclusions

An ideal marker for bacterial infections should allow an early diagnosis and should inform about the course and prognosis of the disease. The current hype on ProCT has indeed a solid scientific basis, since ProCT covers these features better than many other markers, such as C-reactive protein and proinflammatory cytokines [42]. ProCT has emerged as reliable marker and important mediator of sepsis.

Most sepsis is caused by respiratory tract infections (RTI). A ProCT-based therapeutic strategy can reduce antibiotic usage in RTIs, using a new rapid and sensitive assay. A recent meta-analysis confirmed the higher sensitivity and specificity as compared to CRP both for differentiating bacterial infections from non-infective causes of inflammation and for differentiating bacterial infections from viral infections. Thus ProCT provides hope, for an improved diagnostic assessment, antibiotic stewardship and ultimately prognosis of bacterial infections. In addition, being a hormokine mediator, immunoneutralisation of ProCT might open new therapeutic avenues for new treatment options in sepsis.

Beyond any doubt, the diagnosis of infections will continue to require a critical clinical awareness, careful patient history, dedicated physical examination, and appropriate cultures in all patients. However, the interpretation of the clinical response to a bacterial infection lacks standardisation and validation and is, therefore, prone to inter-observer variability [76]. In this context, the measurement of ProCT is considerably more, namely, a standardised and evidence-based method for the assessment of patients with suspected bacterial infections. Accordingly, one should question the routine use of "traditional" markers of inflammation (eg white blood cell count, CRP) for which data on diagnostic accuracy are mostly disappointing, if available at all.

Conversely, ProCT is less than a perfect marker for bacterial infection and we oppose the uncontrolled use of procalcitonin as a substitute for a careful clinical assessment.

Importantly, any observational study investigating the diagnostic accuracy of a given marker is biased by the choice of the "gold standard". In infections this gold standard does not exist, and thus, all studies are prone to a potential bias. Despite decades of research, this problem has not been solved. Importantly, interventional studies, in which the antimicrobial therapy is guided by the marker and in which the gold standard is the outcome, have the potential to resolve this dilemma. The time has arrived, to conduct more intervention studies for other sites of infection, using more sensitive ProCT assays or other, possibly superior, biomarkers to tackle the vicious cycle of antibiotic overuse and emerging multi-resistance.

Correspondence:
Beat Müller, MD
University Hospitals
Petersgraben 4
CH-4031 Basel
Switzerland
E-Mail: Happy.Mueller@unibas.ch
References


Procalcitonin in bacterial infections – hype, hope, more or less?


What Swiss Medical Weekly has to offer:

• SMW’s impact factor has been steadily rising, to the current 1.537
• Open access to the publication via the Internet, therefore wide audience and impact
• Rapid listing in Medline
• LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)
• No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
• Peer review based on a broad spectrum of international academic referees
• Assistance of our professional statistician for every article with statistical analyses
• Fast peer review, by e-mail exchange with the referees
• Prompt decisions based on weekly conferences of the Editorial Board
• Prompt notification on the status of your manuscript by e-mail
• Professional English copy editing
• No page charges and attractive colour offprints at no extra cost

The many reasons why you should choose SMW to publish your research

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

All manuscripts should be sent in electronic form, to:
EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch